



## UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF  
CHEMICAL SAFETY AND  
POLLUTION PREVENTION**MEMORANDUM****Date:** 03/03/2016**SUBJECT:** Bensulide. Human Health Risk Assessment to Support Registration Review.**PC Code:** 009801**Decision No.:** 507866**Petition No.:** NA**Risk Assessment Type:** Single chemical/aggregate**TXR No.:** NA**MRID No.:** NA**DP Barcode:** D428598**Registration No.:** 10163-200**Regulatory Action:** Registration Review**Case No.:** 2035**CAS No.:** 741-58-2**40 CFR:** 180.241**FROM:** Ideliz Negrón-Encarnación, Ph.D., Chemist, RAB V

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## 1.0 Executive Summary

Bensulide is an organophosphate (OP) herbicide registered for food/feed uses on bulb onion, garlic, shallots, leafy vegetable except brassica (crop group (CG) 4), leafy brassica vegetable (CG 5), fruiting vegetable (CG 8), cucurbit vegetable (CG 9), and a regional registration for use on carrots. Tolerances ranging from 0.10 to 0.15 ppm are established in the 40 CFR §180.241 for residues of bensulide, including its oxygen analog, in/on these raw agricultural commodities (RACs). The emulsifiable concentrate (EC) end-use product Prefar 4E (EPA Reg. No. 10163-200) is the only bensulide end-use product registered for use on food/feed crops, which is typically applied to the soil preplant or preemergence using ground equipment. In addition, bensulide is used for weed control in residential and occupational settings, and can be applied to golf courses and residential turf. Based on the registered use pattern for bensulide, humans may be exposed to bensulide in food and drinking water. Dermal and inhalation exposures are anticipated for residential and occupational handlers. In addition, dermal and incidental oral exposures are anticipated from post-application activities occurring in treated areas. There is also the potential for non-occupational exposure as a result of spray drift.

### Hazard Assessment

Bensulide is a member of the organophosphate class of pesticides. Like other OPs, the initiating event in the adverse outcome pathway (AOP)/ mode of action (MOA) for bensulide involves inhibition of the enzyme acetylcholinesterase (AChE) via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system. For bensulide, AChE inhibition is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. Bensulide requires metabolic activation to an oxon to effectively inhibit AChE. OPs also exhibit steady-state AChE inhibition. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. As such, the endpoint selection for bensulide focuses on acute, single day effects and steady-state effects.

The toxicology database for bensulide is complete for risk assessment, except for the requirement of a repeat dose inhalation toxicity study (Leshin, 2015, TXR # 0057280) and bensulide oxon comparative cholinesterase assays (CCA). Appropriate database uncertainty factors are applied for the lack of the inhalation study, and the oxon is considered to be 50X as potent as the parent in the absence of data (see section 4.6.2 for the rationale for 50X).

Bensulide has high quality dose-response data across multiple lifestages and durations via the oral route for both red blood cell (RBC) and brain AChE inhibition (ChEI). Dermal route-specific endpoints could not be evaluated using benchmark dose (BMD) analysis, since the ChEI data from the dermal toxicity study would not model (no apparent dose response). An inhalation study is not available. Clinical signs of neurotoxicity, such as tremor, occur at doses much higher than those causing inhibition of AChE.

The RBC AChE was generally more sensitive than the brain AChE to bensulide. The available AChE data across multiple lifestages (adults, pregnant adults, fetuses, juveniles) demonstrate that the PND 11 pups were generally more sensitive than the adult. In the gestational CCA, the fetus

was not more sensitive than the dam. The pregnant female in the gestational CCA was not more sensitive than the non-pregnant female in the repeated dose CCA. The adult female was typically more sensitive than the adult male, while the pup and fetus did not demonstrate sex-sensitivity.

Bensulide is classified as “not likely to be carcinogenic in humans”, based on an absence of significant tumor increases in two adequate rodent carcinogenicity studies. A quantitative cancer risk assessment is not required. In acute oral lethality studies, bensulide is Toxicity Category II. The acute lethal toxicity is low for other routes, Toxicity Category III or IV for dermal and inhalation toxicity; and dermal and eye irritation. It is not a dermal sensitizer.

*Endpoints and Uncertainty Factors for Risk Assessment:* The endpoint for all exposure scenarios is RBC ChEI and points of departure (PODs) were selected from high quality, well-conducted CCA rat studies. A POD for the acute dietary (all populations) exposure scenario was 11 mg/kg/day; the POD for the steady-state dietary exposure, incidental oral, dermal, and inhalation scenarios was 6 mg/kg/day. The FQPA safety factor (10X) has been retained for infants, children, youths, and women of child-bearing age for all exposure scenarios (both occupational and residential) due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see section 4.4). Additionally, for inhalation exposures, a database uncertainty factor of 30X was applied due to uncertainty in the human dose-response relationship for neurodevelopmental effects and lack of an inhalation toxicity study. For all exposure scenarios, interspecies (10X) and intraspecies (10X) uncertainty factors were applied in addition to the FQPA safety factor. As a result, a total uncertainty factor of 1000X was applied for all non-cancer exposure scenarios, except dietary exposures for the adult population subgroup 50-99 years old (total uncertainty factor = 100X) and inhalation exposures (total uncertainty factor = 3000X).

### **Dietary Exposure and Risk**

Acute and steady state dietary exposure assessments incorporated USDA Pesticide Data Program (PDP) monitoring data for bensulide and its oxon (when available), anticipated residues, default DEEM processing factors, and percent crop treated (CT) data. The Environmental Fate and Effects Division (EFED) provided daily time series outputs for the scenarios that provide the highest and lowest estimated drinking water concentrations (EDWC); groundwater in North Carolina Eastern Coastal Plain (Cotton) and surface water in California (Avocado), respectively. These concentrations were reported as the oxon and converted to bensulide using a 50x factor.

*Acute Dietary Exposure Assessment:* Acute dietary assessments were conducted for food only, water only, and food and drinking water. The acute dietary exposure estimates from food alone are below HED's level of concern (<100 % of the acute population adjusted dose (aPAD)) at the 99.9<sup>th</sup> percentile of exposure, e.g. 46% of the aPAD for the most highly exposed population subgroup, children 3-5 years old. For food and drinking water, the dietary exposure is >10,000% and >1,600% of the aPAD at the 99.9<sup>th</sup> percentile of exposure using drinking water scenarios that provided the highest and lowest EDWC, respectively. Although for Adults 50-99 years old the FQPA SF is 1x, exposures were also of concern for food and drinking water.

*Steady-state Dietary Exposure Assessment:* Steady-state assessments were conducted for food only, water only, and food and drinking water. The steady-state dietary exposure estimates from

food alone are below HED's level of concern (<100 % of the steady-state population adjusted dose (ssPAD) at the 99.9<sup>th</sup> percentile of exposure, e.g. 80% of the ssPAD for the most highly exposed population subgroup, children 3-5 years old. For food and drinking water, the dietary exposure is >10,000% and >2,900% of the ssPAD at the 99.9<sup>th</sup> percentile of exposure using drinking water scenarios that provided the highest and lowest EDWC, respectively. Although for Adults 50-99 years old the FQPA SF is 1x, exposures were also of concern for food and drinking water.

### **Residential Exposure and Risk**

Residential handler risk estimates for applying liquid and granule products to residential lawns are of concern at currently labeled use rates. For residential handlers, a total aggregated risk index (ARI) was used since the LOCs for dermal exposure (1000) and inhalation exposure (3000) are different. The target ARI is 1; therefore, ARIs of less than 1 are risk estimates of concern. Residential post-application risk estimates for turf uses were assessed using chemical-specific turf transferable residue (TTR) data for a liquid formulation, and accounting for the difference in toxicity between the parent, bensulide, and the oxon (i.e., by applying a 50x toxicity adjustment factor). Risk estimates are of concern for dermal exposure for adults and children conducting activities on treated turf; for dermal exposure for adults and youths golfing; for hand-to-mouth exposure for children on treated turf; and for episodic granule ingestion exposure.

### **Non-Occupational Exposure and Risk (Spray Drift and Bystander Volatilization)**

*Spray Drift:* Risk estimates related to spray drift are of concern at various distances from the edge of the field for adults and children (1 to <2 years) depending on the spray drift scenario. For adults, the screening level scenario indicates the LOC is exceeded at a distance of less than 25 feet for applications to vegetables and less than 75 feet for applications to golf courses. For children, the screening level scenario indicates the LOC is exceeded at a distance of less than 75 feet for applications to vegetables and less than 150 feet for applications to golf courses. Drift reduction technologies, such as using coarser sprays and lowering boom height for groundboom sprayers, reduces risk concerns; however, there are still risk estimates of concern at the field edge in some cases.

*Volatilization/Residential Bystander:* Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis, and during Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies) or further analyses are required for bensulide.

### **Aggregate Exposure and Risk**

Because there are risks of concern for the residential and drinking water exposure scenarios, a steady-state aggregate assessment was not conducted. The acute aggregate assessment consists of exposure through food and drinking water and is, therefore, reflected by the acute dietary exposure assessment.

### **Occupational Exposure and Risk**

Occupational handler risk estimates (combined dermal + inhalation) were calculated for the registered uses on golf courses, turf, and vegetable crops. With the label-required personal

protective equipment (PPE), all combined handler risk estimates are of concern. Even with applying maximum PPE or engineering controls, many occupational handler risk estimates remain of concern. Since bensulide is applied to vegetables as a preplant or preemergence application only, occupational post-application dermal exposures are not anticipated for these uses. A quantitative occupational dermal post-application exposure assessment was, therefore, only conducted for the registered golf course use. Occupational post-application dermal risk estimates during maintenance activities on golf courses were of concern (i.e., MOEs are < 1,000) until 5 days after treatment.

### **Human Studies Review**

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. Additional information on how these studies are considered can be found in Appendix C.

## **2.0 HED Recommendations**

The hazard/toxicity, residue chemistry, occupational and residential databases are considered complete with the exception of the data requirements specified in Section 2.1. In addition, label recommendations are discussed in section 2.3.

### **2.1 Data Deficiencies**

*Hazard/Toxicity:* A repeat dose inhalation toxicity study (Leshin, 2015, TXR # 0057280) and bensulide oxon comparative cholinesterase assays (CCA) are required.

*Residue Chemistry:* (1) Three geographically representative field trials on non-bell peppers are required. Pending the submission of these data, the instructions for application to non-bell peppers should be removed from the label. This data deficiency was identified in the bensulide residue chemistry chapter in support of the Registration Eligibility Decision (RED; C. Eiden, D238417, 10/06/1997) and the registration review scoping document (T. Goodlow, D347549, 06/10/2008). (2) Twelve crop field trials for bensulide on tomato grown in Mexico were required in the bensulide residue chemistry chapter in support of the Registration Eligibility Decision (RED; C. Eiden, D238417, 10/06/1997). The label from Mexico was submitted and describes a similar use pattern with the one registered in the US. The registrant expressed their intent to submit a proposal to address this data gap (conference call on 11/16/2015, coordinated by Margaret Hathaway). Pending the submission of these data, the twelve crop field trials are still required.

*Occupational and Residential:* There are no data deficiencies. Chemical-specific turf transferable residue (TTR) data are available; DFR data are not required based on the registered use pattern.

## 2.2 Tolerance Considerations

### 2.2.1 Enforcement Analytical Method

Adequate methods are available for tolerance enforcement for plant commodities. The Pesticide Analytical Manual (PAM) Vol. II lists Gas Chromatography (GC) Method I, using either phosphorus-sensitive thermionic detection or flame photometric detection, for the determination of bensulide and bensulide oxygen analog in plant commodities. Thin layer chromatography (TLC) Method A is available for confirmation. Moreover, the PAM (Volume I, Appendix I) indicates that bensulide is recovered using Multiresidue Methods Sections 302 (Luke Method; Protocol D), 304 (Mills Method; Protocol E, fatty foods) and 303 (Mills, Onley, Gaither Method; Protocol E, non-fatty foods). No information regarding the recovery of bensulide oxygen analog using Multiresidue Methods is included in the PESTDATA database.

### 2.2.2 Recommended Tolerances

HED recommends modifying the tolerance expression and crop groups included in the CFR for bensulide. The tolerance expressions in the 40 CFR § 180.241 (a) and (c) need to be modified to include both coverage and compliance statements for enforcement purposes, as recommended in the Interim Guidance on Writing Tolerance Expressions (S. Knizner, 05/27/2009). The recommended tolerance expressions are:

(a) *General*. “Tolerances are established for residues of the herbicide bensulide, including its metabolites and degradates, in or on the commodities in the following table. Compliance with the tolerance levels specified in the table below is to be determined by measuring only bensulide, S-(O,O-diisopropyl phosphorodithioate) ester of N-(2-mercaptoethyl) benzenesulfonamide, and its oxygen analog, S-(O,O-diisopropyl phosphorothioate) of N-(2-mercaptoethyl) benzenesulfonamide, in or on the commodity.”

(c) *Tolerance with regional registration*. “Tolerances with regional registration, as defined in §180.1(l), are established for residues of the herbicide bensulide, including its metabolites and degradates, in or on the commodities in the following table. Compliance with the tolerance levels specified in the table below is to be determined by measuring only bensulide, S-(O,O-diisopropyl phosphorodithioate) ester of N-(2-mercaptoethyl) benzenesulfonamide, and its oxygen analog, S-(O,O-diisopropyl phosphorothioate) of N-(2-mercaptoethyl) benzenesulfonamide, in or on the commodity.”

Since non-bell pepper field trial data are not available, HED concludes that the tolerance for fruiting vegetable crop group 8 should be deleted and those for bell pepper and tomatillo established in support of domestic registrations. Additional data are required to support a tolerance for tomato imported from Mexico. The establishment of a tolerance for tomato may be recommended if these data (or registrant proposal) are received from the registrant and considered adequate to support this use. Tolerances included in the 40 CFR 180.241 need to be modified as specified in the table below.

<b>Table 2.2.2. Tolerance Summary for Bensulide.</b>			
<b>Commodity</b>	<b>Established Tolerance (ppm)</b>	<b>HED-Recommended Tolerance (ppm)</b>	<b>Comments (correct commodity definition)</b>
Vegetable, fruiting, group 8	0.10	Remove	
Pepper, bell	None	0.10	
Tomatillo	None	0.10	
Tomato, subgroup 8-10A*	None	0.10	

\*May be established pending review of required data in support of import use.

### 2.2.3 International Harmonization

There are no Codex, Mexican or Canadian maximum residue limits established for bensulide. Therefore, harmonization is not germane to this assessment.

## 2.3 Label Recommendations

### 2.3.1 Recommendations from Residue Reviews

A summary of the risk estimates has been provided, and shows that there are dietary risk estimates of concern for registered uses of bensulide. The following recommendations are based on the review of the label of bensulide's end use product Prefar 4-E (EPA Reg. No. 10163-200, 12/13/2013):

- The current label of Prefar 4-E includes instructions for use on non-bell peppers such as chili peppers, cooking peppers, pimientos and sweet peppers. A magnitude of residue study for bensulide in/on non-bell peppers has been required in the RED and scoping document. Alternatively, it was indicated that the registrant could restrict use to bell peppers. Since these data have not been received, HED recommends that the bensulide product label restrict the use to only bell peppers. Moreover, reference to the fruiting vegetables crop group needs to be removed.
- The maximum seasonal application rate for cucurbit vegetables, tomatillo and bell peppers needs to be specified on the label of Prefar 4-E. A maximum seasonal application rate of 6 lbs ai/A is supported by adequate data for crops under these crop groups.

### 2.3.2 Recommendations from Occupational Assessment

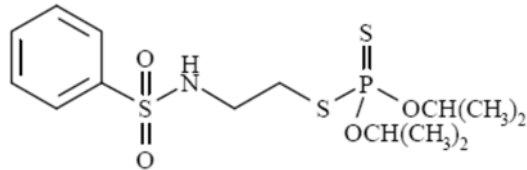
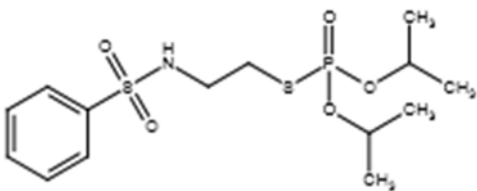
No label recommendations based on the occupational assessment have been identified. A summary of the risk estimates has been provided, and shows that there are risk estimates of concern for registered uses of bensulide based on the use information, label-required personal protective equipment (PPE), and REIs (golf course uses only).

### 2.3.3 Recommendations from Residential Assessment

No label recommendations based on the residential assessment have been identified. A summary of the risk estimates has been provided, and shows that there are risk estimates of concern for registered uses of bensulide based on the current use information.

## 3.0 Introduction

### 3.1 Chemical Identity

Table 3.1. Bensulide and Bensulide Oxon Nomenclature.	
Compound	Chemical Structure
	
Common name	Bensulide
IUPAC name	O,O-diisopropyl-S-2-phenylsulfonylaminoethylphosphorodithioate
CAS name	S-(O,O-diisopropyl phosphorodithioate) ester of N-(2-mercaptoethyl) benzenesulfonamide
CAS #	741-58-2
Compound	Chemical Structure
	
Common name	Bensulide Oxon
IUPAC name	O,O-diisopropyl-S-2-phenylsulfonylaminoethylphosphorothioate
CAS name	S-(O,O-diisopropyl phosphorothioate) of N-(2-mercaptoethyl) benzenesulfonamide
CAS #	20243-81-6

### 3.2 Physical/Chemical Characteristics

The physicochemical properties of bensulide and its oxon are summarized in Appendix B. Bensulide (5.6 mg/L) is moderately soluble in water; however, it is less soluble than its oxon (461 mg/L, EPISuite v. 4.10). Both compounds have low volatility and the oxon has a low partition coefficient. Bensulide is slightly mobile in the four soils tested ( $K_{oc}$ 's ranged from 1,433 to 4,326 mL/g) based on an acceptable study; however, its major degradate bensulide oxon (average  $K_{oc}$  = 557) ranged from moderately mobile to highly mobile in the same four test soils.

### 3.3 Pesticide Use Pattern

Bensulide is used for weed control in residential and occupational settings. Bensulide can be applied to vegetable crops, golf courses, and residential turf. Prefar 4 E (EPA Reg. No. 10163-200) is the only bensulide end-use product registered for food uses on bulb onion, garlic, shallots, leafy vegetable except brassica (CG 4), leafy brassica vegetables (CG 5), fruiting vegetable (CG 8), cucurbit vegetables (CG 9), regional use on carrots grown in Texas, as well as non-food uses on golf courses and home lawns. A summary of bensulide uses is listed in Table 3.3.

<b>Table 3.3. Summary of Directions for Use of Bensulide.</b>					
<b>Applic. Timing, Type, and Equip.</b>	<b>Formulation [EPA Reg. No.]</b>	<b>Applic. Rate (lb ai/A)</b>	<b>Max. Seasonal Applic. Rate (lb ai/A)</b>	<b>PHI (days)</b>	<b>Use Directions and Limitations</b>
<b>Turf (Golf Courses and Residential Lawns)</b>					
Groundboom or low pressure turfgun, Handwand for spot treatment Watered in	Liquid 4 lb ai/gal (46% ai) EPA Reg. No. 2217-696	12.5 lb ai/acre	25 lb ai/acre	NA	PPE: baseline, gloves, PF5 respirator
Tractor drawn spreader, Push type spreader Watered in	Granular 7% ai EPA Reg. No. 2217-778	12.6 lb ai/acre	25.2 lb ai/acre	NA	PPE: Loaders, spreader applicator: Coveralls, gloves, PF5 respirator All others: baseline, gloves For hire applicators must wear PF5 respirator Cannot be applied aerially
Only on lawns Push type spreader only	Granular 3.6% ai EPA Reg. No. 2217-838	12.5 lb ai/acre	NA	NA	No PPE listed Hand-held rotary broadcast spreader prohibited
Tractor drawn spreader, push type spreader	Granular 8.5% ai EPA Reg. No. 9198-172	12.4 lb ai/acre	NA	NA	PPE: loaders, spreader applicator: coveralls, gloves, PF5 respirator All others: baseline, gloves
Golf courses only Tractor drawn spreader or push type spreader Watered in	Granular 5.25% ai EPA Reg. No. 9198-176	16 lb ai/acre	32 lb ai/acre	NA	Not for sale or use by homeowners PPE: push spreaders and loader: coveralls, gloves, PF5 respirator Other applicators: baseline, gloves For hire applicators must wear PF5 respirator
Golf courses only Groundboom, low pressure turfgun, LP Handwand for spot treatment	Liquid 46.4% ai 4 lb ai/gal EPA Reg. No. 10163-196	12.5 lb ai/acre	25 lb ai/acre	NA	PPE: Mixer/loader: baseline, gloves, PF5 respirator Applicator and other: baseline, gloves; for hire applicators must wear PF5 respirator
Golf courses only Watered in	Granular 12.5% ai EPA Reg. No. 10163-198	12.5 lb ai/acre	25 lb ai/acre	NA	PPE: Loaders, spreader applicator: coveralls, gloves, respirator Other applicators: baseline, gloves, respirator
Golf courses only Tractor drawn	Granular 3.6% ai	12.5 lb ai/acre	NA	NA	PPE: Loaders and spreader applicators: coveralls, gloves,

Table 3.3. Summary of Directions for Use of Bensulide.					
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
spreader or push-type spreader Watered in	EPA Reg. No. 10163-199				eyewear, for-hire applicators must wear respirator All other applicators: baseline, gloves, respirator Hand-held rotary spreaders are prohibited
Golf courses only Tractor drawn spreader or push-type spreader Watered in	Granular 7% ai EPA Reg. No. 10163-204	12.6 lb ai/acre	25 lb ai/acre	NA	PPE: loaders and spreader applicators: coveralls, gloves, respirator; others: baseline, gloves, for-hire applicators must wear respirator
Residential lawns only RTU Garden hose sprayer	46.4% ai EPA Reg. No. 10163-205	16 fl oz product/ 2500 sq. ft 8.7 lb ai/A	NA	NA	No PPE listed
Cucurbit vegetables					
Groundboom, Chemigation, Handgun  Preplant or preemergence	Emulsifiable Liquid 4 lb ai/gal EPA Reg. No. 10163-200	6 lb ai/acre	NA	NA	PPE: baseline, gloves; Mixers, loaders and commercial applicators must wear a PF5 respirator May not be applied by aircraft
		9 lb ai/acre	NA	NA	SLN label – CA 960003
Brassica (cole) leafy vegetables; leafy vegetables					
Groundboom, Chemigation, Handgun  Preplant or preemergence	Emulsifiable Liquid 4 lb ai/gal EPA Reg. No. 10163-200	6 lb ai/acre	6 lb ai/acre	NA	PPE: baseline, gloves; Mixers, loaders and commercial applicators must wear a PF5 respirator Do not use on spinach or Swiss Chard May not be applied by aircraft
		9 lb ai/acre	9 lb ai/acre	NA	SLN label – NJ 070001
Fruiting vegetables					
Groundboom, Chemigation, Handgun  Preplant or preemergence	Emulsifiable Liquid 4 lb ai/gal EPA Reg. No. 10163-200	6 lb ai/acre	NA	NA	PPE: baseline, gloves; Mixers, loaders and commercial applicators must wear a PF5 respirator May not be applied by aircraft
Carrots					
Groundboom, Chemigation, Handgun  Preplant or Preemergence	Emulsifiable Liquid 4 lb ai/gal EPA Reg. No. 10163-200	5 lb ai/acre	5 lb ai/acre	NA	PPE: baseline, gloves; Mixers, loaders and commercial applicators must wear a PF5 respirator May not be applied by aircraft
Dry Bulb Vegetables					
Groundboom, Chemigation, Handgun	Emulsifiable Liquid 4 lb ai/gal	6 lb ai/acre	6 lb ai/acre	NA	PPE: baseline, gloves; Mixers, loaders and commercial applicators must wear a PF5 respirator

<b>Table 3.3. Summary of Directions for Use of Bensulide.</b>					
<b>Applic. Timing, Type, and Equip.</b>	<b>Formulation [EPA Reg. No.]</b>	<b>Applic. Rate (lb ai/A)</b>	<b>Max. Seasonal Applic. Rate (lb ai/A)</b>	<b>PHI (days)</b>	<b>Use Directions and Limitations</b>
Preplant or Preemergence	EPA Reg. No. 10163-200				May not be applied by aircraft

NA = Not Applicable for preplant application or application preemergence of the crop.

### 3.4 Anticipated Exposure Pathways

Humans may be exposed to bensulide in food and drinking water because this chemical may be applied directly to growing crops and application may result in bensulide reaching surface and ground water sources of drinking water. Conversion of bensulide into bensulide oxon (13.8%) has been observed under aerobic soil conditions while bensulide may be totally converted into bensulide oxon during the chlorination processes (Kamel et al.; 2009). Moreover, the oxon has been observed in samples of lettuce and carrot. There are residential uses of bensulide for weed control; residential handlers may be exposed during application, and adults and children may be exposed after application in treated areas. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. Since bensulide is applied to crops preplant or preemergence, occupational post-application exposure is not anticipated from those registered uses. However, there is a potential for post-application exposure for workers performing activities in treated golf courses.

### 3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (<http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf>). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the National Health and Nutrition Survey/What We Eat in America (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

#### 4.0 Hazard Characterization and Dose-Response Assessment

Bensulide is a member of the organophosphate class of pesticides. Like other OPs, the initiating event in the adverse outcome pathway (AOP), also often called the mode of action (MOA), for bensulide involves inhibition of the enzyme acetylcholinesterase via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system (see Figure 1). For bensulide, acetylcholinesterase inhibition (ChEI) is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. ChEI is the focus of this hazard characterization; the availability of reliable ChEI dose-response data is one of the key determinants in evaluating the toxicology database.

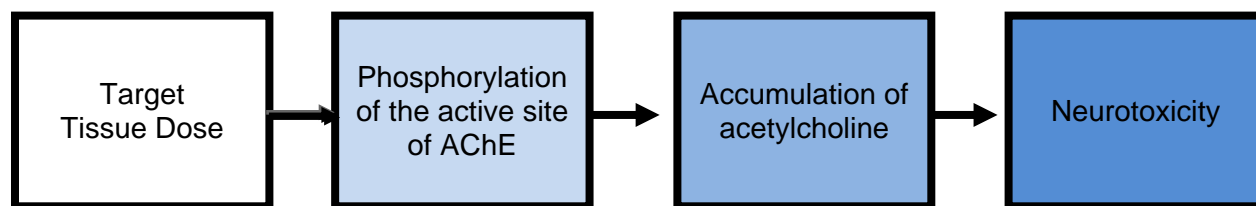


Figure 1. Adverse outcome pathway for OPs

#### 4.1 Toxicology Studies Available for Analysis

The database is considered complete for risk assessment, with the exception of a repeat dose inhalation toxicity study and a bensulide oxon CCA (data gaps). The Health Effect Divisions (HED's) Hazard Science Policy Council (HASPOC) determined, based on a weight of evidence (WOE) approach that a subchronic inhalation toxicity study is required for bensulide due to unacceptable inhalation risk estimates using the current POD from an oral study (Leshin, 2015, TXR # 0057280). The HASPOC also determined that the immunotoxicity study is not required for bensulide (Van Alstine, 2013; TXR # 0056738), as well as the 6-month ocular toxicity study in the dog, and developmental and subchronic neurotoxicity studies (Leshin, 2015, TXR # 0057280). Although oxon CCA data are not available for bensulide, EPA plans to move forward with the bensulide human health risk assessment without toxicity data for bensulide's oxon degradate. In lieu of bensulide-specific oxon CCA data, EPA will use an oxon toxicity adjustment factor of 50X in its calculations (see section 4.6.2 for the rationale for 50X). This value considers the data derived toxicity adjustment factor (TAF) EPA has identified among oxon metabolites for other organophosphates, with an additional margin of safety included due to the uncertainty in extrapolating oxon potency data across chemicals. Toxicology data requirements and confirmation that bensulide meets these requirements are presented in Appendix A.1. The toxicology database includes the following toxicity studies:

- Subchronic oral in rat, mouse, and dog
- 21-day dermal in rat (two studies)
- Developmental in rat and rabbit
- 2-generation reproduction in rat
- Chronic oral in dog, mouse (carcinogenicity), and rat (combined chronic toxicity/carcinogenicity)

- Acute neurotoxicity in rat; delayed neurotoxicity study in hen, comparative cholinesterase assay (CCA) study (gestational, repeated-dose, and acute) in parent but not oxon
- Other studies, such as mutagenicity battery, acute 6-pack, and metabolism study

## 4.2 Absorption, Distribution, Metabolism, and Elimination (ADME)

Bensulide is a phosphorothioate and needs to be bioactivated *in vivo* to its oxygen analog to exert its toxic action (see chemical structure in Table 3.1.1). Seven days after a single oral dose of  $^{14}\text{C}$ -bensulide to rats, radioactivity was excreted primarily in the urine in males (70.2-78.6% of administered dose [AD]) and females (75.2-88.4% AD), with the rest being in the feces (13.6-22.4% AD in males, 8.3-19.6% AD in females). Females excreted the radioactivity faster than males: the females' excretion was almost complete 48 hours after dosing, whereas the males had excreted about 65-70% of the radioactivity at that time. Biliary excretion is minimal. Seven days after administration, the highest concentration of radioactivity in selected tissues in the ADME study was found in whole blood, associated with the cellular component. Whole body autoradiography showed a much higher level of radioactivity remaining in males after 24 hours than in females. Four metabolites were identified. One was the primary urinary metabolite and the other identified metabolites were found in the feces. The proposed formation of two metabolites involved the cleavage of the  $\text{PO}_2[\text{CH}(\text{CH}_3)_2]_2$  moiety of bensulide, followed by methylation and oxidation of the sulphur atom. Conjugation with glycine or carboxylation and oxidative desulphuration is proposed to lead to the other two identified metabolites.

### 4.2.1 Dermal Absorption

Although there are no dermal absorption studies submitted for bensulide, a dermal absorption factor is needed for risk assessment, since the route-specific dermal toxicity study could not be modeled due to a lack of dose response, and an oral endpoint was selected for the dermal exposure assessment. A dermal absorption value of 10% was estimated for dermal risk assessment. This value was derived from a comparison of the effects observed in the oral developmental toxicity (95 mg/kg/day based upon tremors and decreased body weight) and 21-day dermal toxicity studies (1000 mg/kg/day [NOAEL]) in rats.

## 4.3 Toxicological Effects

Bensulide is an OP with a neurotoxic AOP; neurotoxicity is the most sensitive effect in all species, routes, and lifestages and is being used in deriving points of departure (acute = 11 mg/kg/day; steady-state = 6 mg/kg/day). Bensulide has dose response data across multiple lifestages, durations, and routes for both RBC and brain ChEI. Many of these studies have been evaluated using benchmark dose modeling techniques. The CCA, in particular, provided excellent dose-response data for modeling.

Bensulide requires bioactivation to the oxon to allow ChEI; however, no data were submitted regarding the toxicity of the oxon.

The RBC AChE was more sensitive than the brain AChE to bensulide in every analysis (all studies, durations, lifestages, and routes), except the adult males in the acute CCA study. The adult female was typically more sensitive than the male, while the pup and fetus did not demonstrate sex-sensitivity.

Clinical signs of neurotoxicity can be found throughout the database of experimental toxicity studies at doses much higher ( $\geq 95$  mg/kg/day) than those doses causing ChEI. Some of the clinical signs included diarrhea, flaccid abdominal and/or body tone, pinpoint pupils, salivation, lacrimation, decreased respiration, hypothermia, tremors, hypoactivity, dehydration, fur staining, decreased arousal and locomotor activity. No effects were noted on neuropathology; however, bensulide did not induce acute delayed neurotoxicity in the hen.

Although the nervous system was the principal target, the liver was also affected. Liver toxicity (increased organ weight, increased serum ALT, hypertrophy, liver enlargement, liver lipid deposits, pigmentation, and/or vacuolation) was often noted in rat, mouse, and dog at doses of 30 mg/kg/day or greater.

Increased sensitivity was not evident in the developmental studies. No developmental toxicity was observed in the rat at dose levels resulting in maternal toxicity (95 mg/kg/day resulted in tremors and ChEI). Likewise, no developmental toxicity was observed in the rabbit at dose levels resulting in maternal toxicity (80 mg/kg/day resulted in decreased body weights and body weight loss). In the rat 2-generation reproductive toxicity study, systemic toxicity was noted in offspring (93 mg/kg/day resulted in decreased F2 pup survival) at a lower dose than in adults (no systemic toxicity observed). However, ChEI provides the most sensitive endpoint for bensulide, and although ChEI was not measured in pups in the reproduction study, ChEI in adults (occurring at mid- and/or high dose) in this study is protective for the decreased F2 pup survival (as the decrease in survival was noted only at the high dose). In the comparative cholinesterase assays, the ChEI observed in the PND 11 pup was generally greater than the inhibition observed in the adult in both the acute and repeated phases of the CCA study. In the gestational CCA, the fetus was not more sensitive than the dam. The pregnant female in the gestational CCA was not more sensitive than the non-pregnant female in the repeated dose CCA.

Bensulide is classified as “not likely to be carcinogenic in humans” based on the absence of treatment-related tumors in two adequate rodent carcinogenicity studies. There is no mutagenicity concern for bensulide.

The acute (lethal) oral toxicity of bensulide is Toxicity Category II. The acute lethal toxicity is low for other routes, Toxicity Category III or IV for dermal and inhalation toxicity; and dermal and eye irritation. It is not a dermal sensitizer.

More detail concerning the characterization and quantification of the toxic effects of bensulide is provided in Appendix A.2. OPP’s cholinesterase (ChE) policy and use of BMD modeling is also described. A table of the benchmark modeling results is provided in Appendix A.2 (Tables A.2.1 and A.2.2). A toxicity profile table can be found following the benchmark modeling table in Appendix A.2 (Tables A.2.3 and A.2.4). It is noted that the toxicity profile table has not been

updated to include BMD results since these can be found in the previous tables (A.2.1 and A.2.2).

#### 4.3.1 Critical Durations of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. One advantage of an AOP understanding is that human health risk assessments can be refined, focused on the most relevant durations of exposure. Table 4.3.1.1 provides a summary of the selected results from experimental toxicology studies in which ChEI of adult female rat RBC was selected to highlight the effect of duration. Data from the adult female rat RBC ChEI was presented because this sex and compartment were the most sensitive to the effects of bensulide and provided the most data which modeled successfully. Only the BMD<sub>10</sub> results are shown, because the central estimate is used for purposes of comparison according to the BMD guidance.

<b>Table 4.3.1.1. Comparison of Bensulide BMD<sub>10</sub> Results (mg/kg/day) for RBC ChEI over Time in Adult Female Rats</b>		
<b>Duration of dosing</b>	<b>Females BMD<sub>10</sub></b>	<b>MRID#, Test</b>
0.67 days	27.2	49433502, Acute CCA
10 days	18.7	49466201, Repeated Dose CCA
13 days	12.0	49454001, Gestational CCA
13 weeks	9.5	43919601, 13-Week Oral Tox
25 weeks	7.3	44161101, 104-Week Chronic Tox/Carc
51 weeks	4.2	44161101, 104-Week Chronic Tox/Carc
77 weeks	6.6	44161101, 104-Week Chronic Tox/Carc
103 weeks	11.7	44161101, 104-Week Chronic Tox/Carc

CCA = Comparative cholinesterase assay

Tox = Toxicity; Carc = Carcinogenicity

The following text provides an analysis of the temporal pattern of AChE inhibition from acute, single dosing and repeated dosing studies in laboratory animals for bensulide. This analysis provides the basis for determining which exposure durations are appropriate for assessing human health risk.

OPs exhibit a phenomenon known as steady-state ChEI. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of ChEI at a given dose remains relatively consistent across duration. In general, OPs reach steady-state within 2-3 weeks. For bensulide, the results in Table 4.3.1.1 show a pattern of steady-state reached by 13 days of exposure. As demonstrated in the table, the BMDs decrease from acute to repeat exposure, as is typically observed with OP administration. For instance, the BMD<sub>10</sub> in adult female rats was 27 mg/kg in the acute CCA study (oral gavage) and 19 mg/kg/day after 10 days. Although there was variation, this can be expected from using different studies, due to differences in dose selection leading to differences in the quality of modeling. In this case, the BMD<sub>10</sub> after 13 days (12.0 mg/kg/day) is the same as

after 103 weeks (11.7 mg/kg/day). Furthermore, considering the variation in BMD<sub>10</sub> values seen in the bensulide data sets, the BMD<sub>10</sub> after 10 days (18.7 mg/kg/day) can be considered similar to that after 13 days. Thus, in addition to the consistency across durations, the data across multiple studies are similar. Given the results in Table 4.3.1.1, for bensulide, single-day and steady-state durations are appropriate for human health risk assessment. As such, the endpoint selection for bensulide focuses on acute, single-day effects and steady-state effects (10 days and longer).

Although the durations of the toxicity and exposure assessments may differ among the OPs, an exact match is not necessary and would suggest a level of precision that the toxicity data do not support. As such, the single chemical OP assessments will evaluate steady-state, instead of the typical chronic duration dietary assessment. The steady-state point of departure is protective of any exposure duration longer than 10 days for bensulide, including chronic exposure, since cholinesterase inhibition does not increase after reaching maximum inhibition or steady-state.

Although there are data at a shorter time period than 21 days (i.e., 10 days), exposure assessments of 21 days and longer will be conducted for all routes of exposure (i.e., oral, dermal and inhalation) for all single chemical OP assessments. Although the durations of the toxicity and exposure assessments may differ, an exact match is not necessary and would suggest a level of precision that the toxicity data do not support. Given this, the 21-day and longer exposure assessment is scientifically supportable and also provides consistency with the OP cumulative risk assessment (OP Cumulative Risk Assessment (CRA); 2002, 2006) and across the single chemical risk assessment for the OPs.

Given the results in Table 4.3.1.1 above, acute (single day) and steady-state durations are appropriate for human health risk assessment. As such, the endpoint selection focuses on acute, single day effects and steady-state effects. For purposes of consistency with the OP cumulative risk assessment (CRA) and other OPs, exposure assessments of 21 days and longer will be conducted.

#### **4.4 Literature Review on Neurodevelopment Effects**

For the OPs, historically the Agency has used inhibition of AChE as the POD for human health risk assessment; at present time, this policy continues. This science policy is based on decades of work which shows that AChE inhibition is the initial event in the pathway to acute cholinergic neurotoxicity. The use of AChE inhibition data for deriving PODs was supported by the FIFRA SAP (2008, 2012) for chlorpyrifos as the most robust source of dose-response data for extrapolating risk and is the source of data for PODs for bensulide. A detailed review of the epidemiological studies used in this review can be found either in the 2014 chlorpyrifos revised draft human health risk assessment ((D424485, D. Drew et al., 12/29/2014) or in the 2015 literature review for other organophosphates (OPP/USEPA; D331251; 9/15/15).

Newer lines of research on OPs in the areas of potential AOPs, *in vivo* animal studies, and notably epidemiological studies in mothers and children, have raised some uncertainty about the Agency's risk assessment approach with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies have been the subject of review by the Agency over the last several years as part of efforts to develop a risk assessment for chlorpyrifos

(D424485, D. Drew et al., 12/29/2014). Initially, the Agency focused on studies from three US cohorts: 1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University; 2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study or the "Mt. Sinai Child Growth and Development Study;" and 3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. The Agency has evaluated these studies and sought external peer review (FIFRA SAP reviews in 2008 and 2012; federal panel, 2013<sup>1</sup>) and concludes they are of high quality. In the three US epidemiology cohort studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Each of these cohorts evaluated the association between prenatal chlorpyrifos and/or OP exposure (with adverse neurodevelopmental outcomes in children through age 7 years. For the 2014 chlorpyrifos revised human health risk assessment (D424485, D. Drew et al., 12/29/2014), EPA included epidemiologic research results from these three US prospective birth cohort studies but primarily focused on the results of CCCEH since this cohort has published studies on the association between cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The Agency retained the FQPA 10X Safety Factor (SF) in the 2014 chlorpyrifos revised risk assessment, in large part, based on the findings of these studies.

In the 2015 updated literature review (OPP/USEPA; D331251; 9/15/15), the Agency conducted a systematic review expanding the scope of the 2012/2014 review focused on US cohort studies with particular emphasis on chlorpyrifos. The expanded 2015 review includes consideration of the epidemiological data on any OP pesticide, study designs beyond prospective cohort studies, and non-U.S. based studies. The updated literature review identified seven studies which were relevant (Bouchard et al., 2010; Fortenberry et al., 2014; Furlong et al., 2014; Guodong et al., 2012; Oulhote and Bouchard, 2013; Zhang et al., 2014; Shelton et al., 2014). These seven studies have been evaluated in context with studies from the 2012/2014 review (D424485, D. Drew et al., 12/29/2014). Only a brief summary is provided below.

The OP exposure being assessed in many of these studies used concentrations of urinary dialkyl phosphate metabolites (DAPs) as the urinary biomarker. Total DAPs is a non-specific measure of OP exposure and is the sum of six separate molecules - three dimethyl alkylphosphate (DMAP) molecules of DMP, DMTP, DMDTP, and three diethyl alkylphosphate (DEAP) molecules of DEP, DETP, and DEDTP. Each metabolite is a breakdown product from multiple OPs (Table 4.4.-1; CDC, 2008)<sup>2</sup>. Specifically, DMP, DMTP, and DMDTP are associated with 18, 13, and 5 OPs, whereas DEP, DETP, and DEDTP are associated with 10, 10, and 4 OPs, respectively. Thus, using urinary DAPs alone as an exposure measure, it is not possible to separate the exposure and associated effects for single, specific OPs.

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<sup>1</sup> <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170>

<sup>2</sup> [http://www.cdc.gov/nchs/data/nhanes/nhanes\\_03\\_04/126opd\\_c\\_met\\_organophosphorus\\_pesticides.pdf](http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/126opd_c_met_organophosphorus_pesticides.pdf)

**Table 4.4.1.CDC Table of organophosphate pesticides and their dialkyl phosphate metabolites (2008).**

Pesticide	DMP	DMTP	DMDTP	DEP	DETP	DEDTP
Azinphos methyl	X	X	X			
Chlorethoxyphos				X	X	
Chlorpyrifos				X	X	
Chlorpyrifos methyl	X	X				
Coumaphos				X	X	
Dichlorvos (DDVP)	X					
Diazinon				X	X	
Dicrotophos	X					
Dimethoate	X	X	X			
Disulfoton				X	X	X
Ethion				X	X	X
Fenitrothion	X	X				
Fenthion	X	X				
Isazaphos-methyl	X	X				
Malathion	X	X	X			
Methidathion	X	X	X			
Methyl parathion	X	X				
Naled	X					
Oxydemeton-methyl	X	X				
Parathion				X	X	
Phorate				X	X	X
Phosmet	X	X	X			
Pirimiphos-methyl	X	X				
Sulfotepp				X	X	
Temephos	X	X				
Terbufos				X	X	X
Tetrachlorviphos	X					
Trichlorfon	X					

DMP = dimethylphosphate; DEP = diethylphosphate; DMTP = dimethylthiophosphate; DMDTP = dimethyldithiophosphate; DETP = diethylthiophosphate; DEDTP = diethyldithiophosphate.

For studies which measured urinary 3,5,6-trichloro-2-pyridinol (TCPy) (e.g., Fortenberry et al., 2014; Eskenazi et al., 2007; Whyatt et al., 2009), this metabolite can be derived from chlorpyrifos, chlorpyrifos-methyl, and the herbicide triclopyr. TCPy is also the primary environmental degradate of chlorpyrifos, chlorpyrifos-methyl, and triclopyr; thus exposure can be found directly on food treated with these pesticides. CCCEH studies have largely used chlorpyrifos measured in cord blood as the specific biomarker (e.g., Lovasi et al., 2010; Whyatt et al., 2004; Rauh et al., 2011). The CHARGE study (Shelton et al., 2015) did not measure biomarkers but instead used geospatial analysis to focus on the residential proximity to OP exposure using data from the California Department of Pesticide Regulation, with five OPs accounting for a total of 73% of the pesticide applied near residential settings (chlorpyrifos, acephate, diazinon, bensulide, and dimethoate).

Similarly, DAPs can be found directly on food following OP applications (Zhang et al., 2008; Chen et al., 2012). Specifically, studies have shown that DAPs may form as environmental degradates from abiotic hydrolysis, photolysis, and plant metabolism (Zhang et al., 2008; Chen et al., 2012; Racke et al., 1994). Furthermore, since these DAPs are excreted more rapidly and extensively than the parent OPs (Zhang et al., 2008; Forsberg et al., 2008), direct exposure to DAPs may lead to an overestimate of OP exposure when using urinary DAPs as a biomarker of OP exposure. The Agency recognizes that this is a source of uncertainty when using DAPs for assessing OP exposure and will continue to monitor this issue in future assessments.

With respect to neurological effects near birth, the CHAMACOS and Mt. Sinai cohorts measured neurological effects at birth, and observed a putative association with total DEAP, total DMAP, and total DAP exposure (Engel et al., 2007; Young et al., 2005). Similarly, a Chinese study (Zhang et al., 2014) reported statistically significant associations for total DEAPs, total DMAPs, and total DAPs from prenatal OP pesticide exposure and neonatal neurodevelopment assessed 3 days after birth. However, another cross-sectional Chinese study, Guodong et al. (2012), observed no association with urinary DAPs and a developmental quotient score for 23-25 month old children.

The 3 US cohorts (CCCEH, Mt. Sinai, CHAMACOS) each reported evidence of impaired mental and psychomotor development, albeit not consistent by age at time of testing (ranging from 6 month to 36 months across the three cohorts). Attentional problems and ADHD were reported by three prospective cohorts [Rauh et al., 2006; Eskenazi et al., 2007; Marks et al., 2010; and Fortenberry et al. (2014)] investigators with additional support from a case control study, Bouchard et al. (2010). The exposure metric varied among these studies. Specifically, Fortenberry et al. (2014) found suggestive evidence of an association with TCPy and ADHD in boys, whereas statistically significant associations were observed by Rauh et al. (2006) with chlorpyrifos exposure and ADHD. Eskenazi et al. (2007) reported associations with total DMAPs and total DAPs and ADHD; Marks et al. (2010) reported associations with total DEAP, DMAP, and total DAP exposure and ADHD. In a national cross-sectional study of Canadian children, using 2007-2009 data for children age 6-11 years (Oulhote and Bouchard, 2013), there were no overall statistically significant associations observed between child urinary DEAP, DMAP, or total DAP metabolite levels and parentally reported behavioral problems. In contrast, Bouchard et al. (2010), looking at U.S. children age 8-15 years in the 2000-2004 National Health and Nutrition Examination Survey (NHANES), observed a positive association between attention and behavior problems and total DAPs and DMAPs, but not DEAPs. As part of their analysis, Oulhote and Bouchard (2013) noted that their outcome assessment for behavioral problems may not have been as sensitive as Bouchard et al. (2010), which may in part account for the difference in the observed results from these studies.

In addition, the three US cohorts and the CHARGE study have reported suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh et al., 2006; Shelton et al., 2014; Eskenazi et al., 2007; Furlong et al., 2014). Specifically, Furlong et al. (2014) documented suggestive evidence of an association between total DEAP exposure and reciprocal social responsiveness among blacks and boys. Eskenazi et al. (2007) reported a statistically significant association between pervasive developmental disorder (PDD) and total DAP exposure, whereas Eskenazi et al. (2010) reported non-significant, but suggestive, increased odds

of PDD of 2.0 (0.8 to 5.1;  $p=0.14$ ). Rauh et al. (2006) documented a significant association between PDD and specifically chlorpyrifos exposure. Both PDD and reciprocal social responsiveness are related to the autism spectrum disorder. Using a different exposure assessment method (geospatial analysis and residential proximity to total OP exposure), Shelton et al. (2014) also showed statistically significant associations between total OP exposure and ASD. While these studies vary in the magnitude of the overall strength of association, they have consistently observed a positive association between OP exposure and ASD. Finally, CCCEH, Mt. Sinai, CHAMACOS have reported an inverse relation between the respective prenatal measures of chlorpyrifos and intelligence measures at age 7 years (Rauh et al., 2011; Engel et al., 2011; Bouchard et al., 2011).

Across the epidemiology database of studies, the maternal urine, cord blood, and other (meconium) measures provide evidence that exposure did occur to the fetus during gestation but the actual level of such exposure during the critical window(s) of susceptibility is not known. While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the children's health cohorts, it is unlikely that these exposures resulted in AChE inhibition. As part of the CHAMACOS study, Eskenazi et al. (2004) measured AChE activity and showed that no differences in AChE activity were observed. The biomarker data (chlorpyrifos) from the Columbia University studies are supported by the Agency's dose reconstruction analysis using the PBPK-PD model (D424485, D. Drew et al., 12/29/2014). Following the recommendation of the FIFRA SAP (2012), the Agency conducted a dose reconstruction analysis of residential uses available prior to 2000 for pregnant women and young children inside the home. The PBPK-PD model results indicate for the highest exposure considered (i.e., indoor broadcast use of a 1% chlorpyrifos formulation) <1% RBC AChE inhibition was produced in pregnant women. While uncertainty exists as to actual OP exposure at (unknown) critical windows of exposure, EPA believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition.

A review of the scientific literature on potential modes of action/adverse outcome pathways (MOA/AOP)<sup>3</sup> leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the December 2014 chlorpyrifos revised risk assessment (D424485, D. Drew et al., 12/29/2014). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers that include targets other than AChE inhibition, including cholinergic and non-cholinergic systems, signaling pathways, proteins, and others. However, no one pathway has sufficient data to be considered more credible than the others. The fact that there are, however, sparse AOP data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence significantly limits their quantitative use in risk assessment. The SAP concurred with the Agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects. However, since the 2014 literature review, there are no substantive changes in the ability to define and quantitate steps in an MOA/AOP leading from exposure to effects on the developing brain. Published and submitted guideline DNT laboratory animal studies have been reviewed for OPs as part of the 2012/2014 review (D424485, D. Drew

<sup>3</sup> Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events.

et al., 12/29/2014) and the updated 2015 review (OPP/USEPA; D331251; 9/15/15).

Neurobehavioral alterations in laboratory animals were often reported, albeit at AChE inhibiting doses, but there was generally a lack of consistency in terms of pattern, timing, or dose-response for these effects, and a number of studies were of lower quality. However, this information does provide evidence of long-lasting neurodevelopmental disorders in rats and mice following gestational exposure.

At this time, a MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes. This growing body of literature does demonstrate, however, that OPs are biologically active on a number of processes that affect the developing brain. Moreover, there is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure, albeit at doses which cause AChE inhibition. EPA considers the results of the toxicological studies relevant to the human population, as qualitatively supported by the results of epidemiology studies. The Agency acknowledges the lack of established MOA/AOP pathway and uncertainties associated with the lack of ability to make strong causal linkages and unknown window(s) of susceptibility. These uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite all these differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong et al., 2012; Oulhote and Bouchard, 2013), authors have identified associations with neurodevelopmental outcomes associated with OP exposure across four cohorts and twelve study citations. Specifically, there is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increased in some instances), and observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures.

As section 408(b)(2)(C) of the FFDCA instructs EPA, in making its “reasonable certainty of no harm” finding, that in “the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children.” Section 408 (b)(2)(C) further states that “the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.” Given the totality of the evidence, there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the Agency from reducing or removing the statutory 10X FQPA Safety Factor. For the bensulide DRA, a value of 10X has been applied. Similarly, a database uncertainty factor of 10X will be retained for occupational risk assessments. The Agency will continue to evaluate the epidemiology studies and pursue approaches for quantitative or semi-quantitative comparisons between doses which elicit AChE inhibition and those which are associated with neurodevelopmental outcomes prior to a revised human health risk assessment.

#### 4.5 Safety Factor for Infants and Children (FQPA SF)

As noted above, the lack of an established neurodevelopmental MOA/AOP makes quantitative use of the epidemiology studies in risk assessment challenging, particularly with respect to determining dose-response, critical duration of exposure, and window(s) of susceptibility. However, exposure levels in the range measured in the epidemiology studies are likely low enough that they are unlikely to result in AChE inhibition. Epidemiology studies consistently identified associations with neurodevelopmental outcomes associated with OP exposure such as delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children. Therefore, there is a need to protect children from exposures that may cause these effects; this need prevents the Agency from reducing or removing the statutory FQPA Safety Factor. **Thus, the FQPA 10X Safety Factor will be retained for bensulide for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.**

A database uncertainty factor of 30x will be applied to inhalation risk assessment only, to incorporate the uncertainty in the human dose-response relationship for neurodevelopmental effects and for the absence of inhalation data.

##### 4.5.1 Completeness of the Toxicology Database

The database of toxicology studies for bensulide is complete, except for the requirement of a repeat dose inhalation toxicity study. Available bensulide studies include developmental toxicity studies in rats and rabbits, a reproductive toxicity study in rats, an acute neurotoxicity study in rats, and a CCA study in rats [acute (young adult and PND 11 pups)), repeated dose (young adult and PND 11 pups), and gestational (fetus and dam)]. A CCA study for the oxon is not available, and exposure to the oxon is considered to be 50X as toxic as exposure to the parent in the absence of this data.

##### 4.5.2 Evidence of Neurotoxicity

Bensulide is an OP with a neurotoxic AOP; neurotoxicity is the most sensitive effect in all species, routes, and lifestages and is being used to derive PODs for risk assessment. Therefore, the risk assessment is protective of potential neurotoxicity for every life stage and route of exposure.

##### 4.5.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Sensitivity was not evident in the developmental studies. No developmental toxicity was observed in the rat at dose levels resulting in maternal toxicity (tremors and decreased AChE). Likewise, no developmental toxicity was observed in the rabbit at dose levels resulting in maternal toxicity (decreased body weights and body weight loss). In the rat 2-generation reproductive toxicity study, systemic toxicity was noted in offspring (decreased F2 pup survival at the high dose), while no systemic toxicity was noted in adults. However, ChEI provides the most sensitive endpoint for bensulide, and although ChEI was not measured in pups, ChEI in adults in this study (observed at mid and/or high dose) is protective (6.7-fold more sensitive) for

the decreased F2 pup survival. The PND 11 pup was generally more sensitive than the adult in the acute and repeated dose CCA. The CCA study did not demonstrate the fetus to be more sensitive than the dam. Endpoints were chosen to be protective of all lifestages.

As discussed in Section 4.4, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA Safety Factor for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.

#### 4.5.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties with regard to the exposure databases. The acute and steady-state dietary assessment incorporated PDP monitoring data for bensulide and its oxon (when available), anticipated residues, default DEEM processing factors, and percent crop treated (CT). A TAF of 50x was applied to residues of the oxygen analog in food commodities and drinking water, as well as turf transferable residue data used in the residential assessment. Although data were used to refine the acute and steady-state dietary exposure assessments, the assessments are not expected to underestimate dietary (food and water) exposures. The residential handler and post-application exposure assessments are based upon the residential SOPs. The residential SOPs are based upon reasonable worst-case assumptions and are not expected to underestimate risk. These assessments of exposure are not likely to underestimate the resulting estimates of risk from exposure to bensulide.

### 4.6 Toxicity Endpoint and Point of Departure Selections

#### 4.6.1 Dose-Response Assessment

Table 4.6.4.1 summarizes the bensulide toxicity endpoints and PODs selected from an evaluation of the database. This endpoint selection was based on a weight of the evidence evaluation using the following considerations:

- *Relative sensitivity of the brain and RBC compartments:* The **RBC** AChE was more sensitive than the brain AChE to bensulide in every analysis (all studies, durations, lifestages, and routes), except the adult males in the acute CCA study. As such, OPP has relied upon the RBC data in POD derivation.
- *Potentially susceptible populations (fetuses, juveniles, pregnancy, or sex):* The available AChE data across multiple lifestages (adults, pregnant adults, fetuses, juveniles) show that the **PND 11 pups** were generally more sensitive than the adult 1.5-4.5 -fold. In the gestational CCA, the fetus was not more sensitive than the dam. The pregnant female in the gestational CCA is not more sensitive than the non-pregnant female in the repeated dose CCA. The adult female was typically more sensitive than the adult male, while the pup and fetus did not demonstrate sex-sensitivity. See Appendix A.5.
- *Route of exposure:* It is preferred to match, to the degree possible, the route of exposure in the toxicity study with that of the exposure scenario(s) of interest. In the case of bensulide, BMD modeling data are only available for the oral route. The data from the dermal study were not amenable to modeling (no apparent dose response); however, the

dermal absorption is low (DAF = 10%). An inhalation study is not available but is required.

- *Duration of exposure:* It is preferred to match, to the degree possible, the duration of a toxicity study with that of the exposure duration of interest. There are single-day and steady-state oral studies available. Steady-state dermal studies are available, but no inhalation study is available.
- *Consistency across studies:* In cases where multiple datasets are available for a single duration, it is important to evaluate the extent to which data are consistent (or not) across studies. Considering the presence of sensitive populations, that different labs conducted the studies across several years, the bensulide database demonstrated consistent ChEI and effects. In particular, the study protocol and performance of the CCA enable great confidence in the results of this study.

Descriptions of the primary toxicity studies used for selecting toxicity endpoints and points of departure for various exposure scenarios are presented in Appendix 3 of this document. Summary tables of BMD analyses can be found in Appendix 2, and the technical details of the analysis can be found in the BMD memo (Bever, 2015, TXR # 0057236).

Consistent with risk assessments for other AChE-inhibiting compounds, OPP has used a benchmark response (BMR) level of 10% and has thus calculated BMD<sub>10S</sub> and BMDL<sub>10S</sub> (see Appendix A.2. for summary of OPP's ChE policy). The BMD<sub>10</sub> is the estimated dose where ChE is inhibited by 10% compared to background. The BMDL<sub>10</sub> is the lower confidence bound on the BMD<sub>10</sub>. As a matter of science policy, the Agency uses the BMDL, not the BMD, for use as the POD (USEPA, 2012). All BMD/BMDL modeling was completed using USEPA BMD Software, version 2.4; an exponential model or Hill model was used to fit the data.

#### Acute Dietary Endpoint (All Populations)

A POD for the acute dietary (all populations) exposure scenario was derived from the results of a high-quality, well-conducted acute CCA rat study (MRID 49433502). A BMDL<sub>10</sub> of 11 mg/kg was selected and was associated with RBC ChE inhibition in female pups (PND 11). The corresponding BMD<sub>10</sub> was 16 mg/kg. RBC cholinesterase inhibition was selected as the endpoint for the POD, since BMD<sub>10</sub> values were lower than those for brain cholinesterase inhibition. Data from the PND 11 pups are appropriate for acute POD derivation, since effects were observed after a single exposure and the endpoint is the most sensitive adverse response in all populations (infant and children, females 13+, and adults).

An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA safety/ database uncertainty factor due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is applied to the BMDL<sub>10</sub> to obtain an aPAD of 0.011 mg/kg/day for exposure scenarios with infants, children, youths, and women of childbearing age. The only population subgroup for which the FQPA SF is not retained is adults 50-99; therefore, the aPAD for this population subgroup is 0.11 mg/kg/day.

*Steady-State Dietary Endpoint (All Populations)*

A POD for the steady-state dietary (all populations) exposure scenario was derived from the repeated-dose response observed in a CCA rat study (MRID 49466201). A BMDL<sub>10</sub> of 6 mg/kg/day was selected and was associated with RBC ChE inhibition in male pups (PND 11 initially). The corresponding BMD<sub>10</sub> was 8 mg/kg/day. RBC cholinesterase inhibition was selected as the endpoint for the POD, since BMD<sub>10</sub> values were lower than those for brain cholinesterase inhibition. Of the best modeled data sets, data from the PND 11 pups provided the most sensitive adverse response of all populations (infant and children, females 13+, and adults). Discussion of the steady-state POD is provided in Section 4.3.1. The modeling of the CCA study allowed for a much greater confidence in the accuracy of the resulting estimated BMDL<sub>10</sub>. Overall, the CCA study provided the best source of data to establish the steady-state value due to more optimal selection of doses, the number of dose groups (6), sampling at the time of peak effect from a gavage study, several lifestages (adult, PND 11 pups, pregnant dams, fetuses), acute and repeat exposure periods, and the quality of BMD modeling lending confidence to the results. Furthermore, the CCA study allowed the evaluation of the most sensitive life stage (PND 11 pups). The combination of best fit modeling and most protective value occurred for ChE inhibition in the PND 11 male RBC following 10 daily doses (6 mg/kg/day, repeated dose CCA study). The BMD<sub>10</sub> of 8 mg/kg/day from this study fits within the range of that observed at longer durations in the chronic toxicity/ carcinogenicity study.

The endpoint and POD are protective of all other effects observed in the database. An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA safety/ database uncertainty factor due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is applied to the BMDL<sub>10</sub> to obtain a ssPAD of 0.006 mg/kg/day for all exposure scenarios, except adults 50-99. Excluding the FQPA SF for adults 50-99, the ssPAD is 0.06 mg/kg/day.

*Incidental Oral Endpoint/ Steady-State*

A POD of 6 mg/kg/day was selected from the repeat dose CCA study in rats, based on the same rationale provided above for the steady-state dietary exposures. A total uncertainty factor of 1000X is appropriate for incidental oral exposures (10X for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) allowing a Level of Concern (LOC) of 1000X.

*Dermal Endpoints/ Steady-State*

A POD of 6 mg/kg/day was selected from the repeat dose CCA study in rats, based on the same rationale provided above for the steady-state dietary exposures. The POD was adjusted based on a 10% dermal absorption factor to 60 mg/kg/day. A total uncertainty factor of 1000X is appropriate for dermal exposures (10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF for residential assessments or a database uncertainty factor in occupational assessments due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)), allowing a LOC of 1000X.

The ChEI data from the dermal toxicity study would not model due to a lack in dose response. The dermal toxicity study NOAEL from MRIDs 44801101 and 44809401 is 50 mg/kg/day,

which approximates the selected POD of 6 mg/kg/day with the DAF of 10% (i.e. 60 mg/kg/day adjusted dose). The LOAEL was 500 mg/kg/day based on brain ChEI. Due to dose spread issues related to the NOAEL approach and the quality of the BMD analysis from the CCA study, the CCA study is a more appropriate selection than the dermal study. Since plasma and brain ChEI was observed at 500 mg/kg/day, it would be expected that RBC inhibition be observed as well. Therefore, instead of relying on brain ChEI for only the dermal route of exposure, the RBC AChE data from the CCA study can be aggregated with the dermal and inhalation routes.

#### Inhalation Endpoints/ Steady-State

A POD of 6 mg/kg/day was selected from the repeat oral dose CCA study in rats, based on the same rationale provided above for the steady-state dietary exposures. A route-specific inhalation study is unavailable. Toxicity through the inhalation route is considered to be similar to that of the oral route. The total uncertainty factor of 3000X was applied (10X for interspecies extrapolation, 10X for intraspecies variation, and 30X database uncertainty factor incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4) and because there is an unfulfilled inhalation study requirement for bensulide), resulting in a LOC of 3000X.

### **4.6.2 Oxon Toxicity Adjustment Factor**

In the 2006 updated OP cumulative risk assessment (CRA), the Agency characterized the potential impacts of the conversion of OP pesticides to oxon transformation products during standard drinking water treatment processes. For those OP pesticides that could potentially transform into more toxic oxons, the Agency assumed a complete transformation as a result of drinking water treatment. Based on limited data (documented in the 2002 OP CRA), the Agency assumed that the oxons would persist for a sufficient time to travel through the distribution system.

The Agency used submitted data to characterize the relative toxicity differences between the oxon and the parent for some of the OP pesticides; information from published literature was also available to inform relative potency for a few OP Pesticides<sup>4</sup>. For those OP pesticides without sufficient oxon data, the Agency initially used upper bound oxon adjustment factors of 10X and 100X for estimating potential oxon potency. The 100X was used considering the highest relative toxicity difference observed (61X) for malathion/malaoxon, based on the data available at the time. However, since then, acute and repeat dose CCA studies have been submitted for both malathion and malaoxon. The new data allow a direct comparison of relative toxicity for the two chemicals and therefore, reduces uncertainty; an oxon adjustment factor of 22X was determined based on these data. As a result, a 50X oxon adjustment factor has been used for the OP draft risk assessments for registration review to estimate potential oxon potency. The 50X accounts for the highest oxon adjustment factor of 22X with an additional safety margin to protect for potential oxon toxicity for chemicals without oxon data. The adjustment factors were applied to residues for risk assessment of all exposure durations, routes, and scenarios.

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<sup>4</sup> Chambers JE, Carr RL. 1993. "Inhibition patterns of brain acetylcholinesterase and hepatic and plasma aliesterases following exposures to three phosphorothionate insecticides and their oxons in rats." *Fundamental and Applied Toxicology*. Jul;21(1):111\_9.

OP PESTICIDE	OXON ADJUSTMENT FACTOR
Azinphos-Methyl	No data
Bensulide	No data
Chlorethoxyfos	No data
Chlorpyrifos	11.9X (acute); 18X (repeated): RBC
Coumaphos	No data
Diazinon	12.1X (acute); 9.0X (repeated):RBC
Dimethoate	8 X (acute); 3X (repeated): Brain
Disulfoton	No data
Malathion	22X (acute); 22X (repeated): RBC
Methidathion	No data
Methyl Parathion	<10X (Chambers and Carr, 1993)*
Phostebuprim	No data
Propetamphos	No data
Temephos	No data

Oxon toxicity adjustment factors are based on a comparison of the most sensitive compartment (i.e., RBC or brain) determined for the chemical.

#### 4.6.3 Recommendation for Combining Routes of Exposures for Risk Assessment

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major sources (oral, dermal, and inhalation) and determine whether the individual exposures can be combined if they have the same toxicological effects. PODs for the incidental oral, dermal, and inhalation routes are all derived from RBC AChE inhibition. As a result, exposure from all routes can be combined.

#### 4.6.4 Cancer Classification and Risk Assessment Recommendation

Bensulide is classified as a “Group E Chemical – evidence of non-carcinogenicity for humans” based on lack of evidence for carcinogenicity in rats and mice. There is no mutagenicity concern for bensulide.

#### 4.6.5 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

**Table 4.6.5.1 Summary of Toxicological Doses and Endpoints and Points of Departure for Bensulide in Dietary and Non-Occupational Human Health Risk Assessments <sup>a</sup>**

Exposure Scenario	Point of Departure (mg/kg/day)	Uncertainty/FQPA Factors	RfD, PAD, & LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations Except Adults 50-99 Years)	BMDL <sub>10</sub> = 11 mg/kg	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 10x	Acute RfD = 0.11 mg/kg  aPAD = 0.011 mg/kg	Acute CCA Study (MRID 49433502) in the rat BMD <sub>10</sub> = 16 mg/kg  Inhibition of RBC ChE in female pups (PND 11)
Acute Dietary (Adults 50-99 Years)	BMDL <sub>10</sub> = 11 mg/kg	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 1x	Acute RfD = aPAD = 0.11 mg/kg	Acute CCA Study (MRID 49433502) in the rat BMD <sub>10</sub> = 16 mg/kg  Inhibition of RBC ChE in female pups (PND 11)
Steady-State Dietary (All Populations Except Adults 50-99 Years)	BMDL <sub>10</sub> = 6 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 10x	ssRfD = 0.06 mg/kg/day  ssPAD = 0.006 mg/kg/day	Repeated-Dose CCA Study (MRID 49466201) in the rat BMD <sub>10</sub> = 8 mg/kg/day  Inhibition of RBC ChE in male pups (PND 11 initially)
Steady-State Dietary (Adults 50-99 Years)	BMDL <sub>10</sub> = 6 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 1x	ssRfD = ssPAD = 0.06 mg/kg/day	Repeated-Dose CCA Study (MRID 49466201) in the rat BMD <sub>10</sub> = 8 mg/kg/day  Inhibition of RBC ChE in male pups (PND 11 initially)
Incidental Oral Steady-State	BMDL <sub>10</sub> = 6 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 10x	Residential LOC for MOE = 1000x	Repeated-Dose CCA Study (MRID 49466201) in the rat BMD <sub>10</sub> = 8 mg/kg/day  Inhibition of RBC ChE in male pups (PND 11 initially)
Dermal Steady-State	BMDL <sub>10</sub> = 6 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 10x  DAF = 10%	Residential LOC for MOE = 1000x	Repeated-Dose CCA Study (MRID 49466201) in the rat BMD <sub>10</sub> = 8 mg/kg/day  Inhibition of RBC ChE in male pups (PND 11 initially)

**Table 4.6.5.1 Summary of Toxicological Doses and Endpoints and Points of Departure for Bensulide in Dietary and Non-Occupational Human Health Risk Assessments <sup>a</sup>**

Exposure Scenario	Point of Departure (mg/kg/day)	Uncertainty/FQPA Factors	RFD, PAD, & LOC for Risk Assessment	Study and Toxicological Effects
Inhalation Steady-State	BMDL <sub>10</sub> = 6 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 30x <sup>b</sup>	Residential LOC for MOE = 3000x	Repeated-Dose CCA Study (MRID 49466201) in the rat BMD <sub>10</sub> = 8 mg/kg/day  Inhibition of RBC ChE in male pups (PND 11 initially)
Cancer (oral, dermal, inhalation)	Classification: Group E chemical; Evidence of Non-Carcinogenicity in Humans			

<sup>a</sup> Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. BMDL = lower limit of the bench mark dose. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF<sub>A</sub> = extrapolation from animal to human (interspecies). UF<sub>H</sub> = potential variation in sensitivity among members of the human population (intraspecies). SF = Safety Factor. PAD = population adjusted dose (a = acute, ss = steady-state or maximal acetyl cholinesterase inhibition which occurs around 2-3 weeks for most OPs and is a specific exposure assessment conducted for OPs, instead of the traditional short, intermediate, or chronic assessments. The SS assessment is protective of longer durations of exposure, including chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. FQPA = Food Quality Protection Act

<sup>b</sup> This uncertainty factor incorporates uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4) and because there is an unfulfilled inhalation study requirement for bensulide

**Table 4.6.5.2 Summary of Toxicological Doses and Endpoints for Bensulide for Use in Occupational Human Health Risk Assessments <sup>a</sup>**

Exposure/Scenario	Point of Departure	Uncertainty/FQPA Factors	LOC for Risk Assessment	Study and Toxicological Effects
Dermal Steady-State	BMDL <sub>10</sub> = 6 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x UF <sub>DB</sub> = 10x  DAF = 10%	Occupational LOC for MOE = 1000x	Repeated-Dose CCA Study (MRID 49466201) in the rat BMD <sub>10</sub> = 8 mg/kg/day  Inhibition of RBC ChE in male pups (PND 11 initially)
Inhalation Steady-State	BMDL <sub>10</sub> = 6 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x UF <sub>DB</sub> = 30x	Occupational LOC for MOE = 3000x	Repeated-Dose CCA Study (MRID 49466201) in the rat BMD <sub>10</sub> = 8 mg/kg/day  Inhibition of RBC ChE in male pups (PND 11 initially)
Cancer (oral, dermal, inhalation)	Classification: Group E chemical – Evidence of Non-Carcinogenicity in Humans			

<sup>a</sup> Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. BMDL = lower limit of the bench mark dose. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF<sub>A</sub> = extrapolation from animal to human (interspecies). UF<sub>H</sub> = potential variation in sensitivity among members of the human population (intraspecies). LOC = level of concern. UF<sub>DB</sub> = database uncertainty factor

<sup>b</sup> This uncertainty factor incorporates uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4) and because there is an unfulfilled inhalation study requirement for bensulide. Steady-State = steady-state or maximal AChE inhibition which occurs around 2-3 weeks for most OPs and is a specific exposure assessment conducted for OPs instead of the traditional short, intermediate, or chronic assessments. The steady-state assessment is protective of longer durations including chronic.

## 4.7 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic, and chronic durations and assess carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental, and reproductive effects in different taxonomic groups. As part of its reregistration decision for bensulide, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), bensulide is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a “naturally occurring estrogen, or other such endocrine effects as the Administrator may designate.” The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP, where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013<sup>1</sup> and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

<sup>1</sup> See <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074> for the final second list of chemicals.

Bensulide is on List 2. List 2 represents the next set of chemicals for which EPA intends to issue test orders/data call-ins in the near future. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.<sup>ii</sup>

## 5.0 Dietary Exposure and Risk Assessment

### 5.1 Residues of Concern Summary and Rationale

The nature of the residues in plants is adequately established based on carrot, lettuce and tomato metabolism studies. The residues of concern for risk assessment in plants and drinking water, and tolerance enforcement in plants consists of bensulide and its oxon (C. Eiden, D238417, 10/06/1997). Appendix E summarizes the metabolism data for parent bensulide and its oxygen analog.

<b>Table 5.1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression</b>			
Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Bensulide and its oxon	Bensulide and its oxon
	Rotational Crop	NS <sup>1</sup>	NS <sup>1</sup>
Livestock	Ruminant	NR <sup>1</sup>	NR <sup>1</sup>
	Poultry		
Drinking Water		Bensulide and its oxon	Not Applicable

<sup>1</sup> NS = Not specified. It was indicated that the nature of the residue seems to be similar to that on primary crops (C. Eiden, D218575, 04/02/1997). Following the 120-day plant-back interval (PBI), residues in rotational crops do not need to be considered for risk assessment and tolerance enforcement.

<sup>2</sup> NR = Not required to support the established uses of bensulide. Livestock metabolism studies may be required if new uses are sought.

### 5.2 Food Residue Profile

The nature of the residues in plants is adequately established based on carrot, lettuce and tomato metabolism studies. Tolerances are established in the 40 CFR § 180.241 for the use of bensulide on bulb onion, leafy vegetable except brassica (CG 4), leafy brassica vegetables (CG 5), fruiting vegetable (CG 8), and cucurbit vegetables (CG 9), and a regional registration for use on carrots. Uses on garlic and shallots are in the label as well which is covered by the tolerance for bulb onion, refer to the 40 CFR § 180.1. The established tolerances are based on measurement of bensulide and its oxygen analog and range from 0.10 to 0.15 ppm. The 0.10 ppm tolerances are based on combined levels of bensulide and its oxon at the LOQ of 0.05 ppm. However, in order to account for potential residue losses during storage prior to analysis, the tolerance for bensulide residues on brassica vegetables (CG 5), cucurbit vegetables (CG 9) and leafy vegetables (CG 4)

<sup>ii</sup> <http://www.epa.gov/endo/>

is 0.15 ppm (based on twice the limit of quantitation for bensulide *per se* (0.10 ppm) plus the limit of quantification for bensulide oxon (0.05 ppm)).

Metabolism studies conducted with lettuce, carrot and tomato show that parent bensulide was at quantifiable levels only in carrot, while the oxygen analog was quantified in lettuce and carrot, refer to Appendix E. Levels of the oxon were higher than those of parent bensulide only in lettuce, which suggest that the oxon may predominate. Moreover, PDP data for lettuce (years 2010 and 2011) show that bensulide was detected in 6 of 1487 samples whereas bensulide oxon was detected in 49 of those 1487 samples. Generally, the concentration of the oxon in/on lettuce is higher than that of parent bensulide. PDP data for carrots do not show quantifiable residues of bensulide or its oxon while data for tomato do not show residues of bensulide's oxon.

As part of registration review, the residue chemistry database for bensulide was evaluated. The only data deficiency identified in the registration eligibility decision (C. Eiden, D238417, 10/06/1997) that has not been satisfied is additional crop field trials for bensulide on non-bell peppers (domestic use) and tomato (import use). Although these data are not available, the dietary risk is not underestimated since the assessment incorporates anticipated residues for non-bell peppers and tomato.

### 5.3 Water Residue Profile

The drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) in the following memorandum: "Bensulide: Drinking Water Exposure Assessment for Registration Review" (D428601, He Zhong, 09/14/2015) and incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources."

Drinking water from surface water sources may be subjected to water treatment through chlorination. Kamel *et al.* (2009) demonstrated that the parent bensulide residues may be totally converted into bensulide oxon during chlorination processes. Therefore, a total toxic residue (TTR) approach based on the oxon equivalent was used for drinking water from surface water sources. The recommended estimated drinking water concentrations (EDWCs) of the TTRs from surface water sources were generated with the Surface Water Concentration Calculator (SWCC) model from the use scenario of the maximum exposure, California lettuce, with three ground spray applications at 6 lb ai/A each and a minimum 4-month interval (Table 5.3.1).

Drinking water from groundwater sources is seldom subjected to chlorination; thus, conversion of bensulide to its oxon was only based on aerobic soil metabolism processes (13.8%). Therefore, recommended oxon EDWCs from groundwater sources were modeled with PRZM-GW based on the oxon soil conversion rate at 2.12 lbs ai per acre following the use scenario on loamy sand soil in NC eastern coastal plain with two single bensulide maximum granular applications at 16 lb ai per acre each at 4-month intervals (Table 5.3.1). Note that the EDWCs for groundwater were also obtained by modeling bensulide at the maximum application rate; however, the EDWCs recommended by EFED are based on the oxon since these were higher than those for parent bensulide. Based on modeling, the highest residues were obtained for

groundwater. In addition, the scenario that provided the lowest EDWC (California Avocado; 3 applications at 6 lbs ai/A) was modeled to provide the lowest estimate of the exposure and risk for food and drinking water, see Table 5.3.2.

<b>Table 5.3.1. Recommended Surface water and Groundwater EDWCs (µg/L) for Bensulide Oxon</b>			
Surface Water Model: Tier II SWCC (v 1.106)			
	1 in 10 yr Peak	1 in 10 yr Annual Average	30 yr Annual Average
Ground Spray - CA Lettuce scenario (W23273.dvf) (6 lbs ai/acre for 3 applications (2/1, 6/1, 10/1))	979	494	305
Groundwater Model: Tier 1 PRZM-GW			
	Peak Values	Post Breakthrough Average	Breakthrough Time (Days)
NC Eastern Coastal Plain - (w13722Extended.dvf) 2.12 lbs ai/acre for 2 applications (3/1 and 7/1)	<b>1,250</b>	<b>1,200</b>	7,106

<b>Table 5.3.2. Surface Water EDWCs for Bensulide TTRs</b>			
Scenario	Concentration (µg/L)		
	1 in 10 yr Peak	1 in 10 yr Annual Average	30 year Annual Average
CA Avocado (W23188.dvf)	179	100	73

For the acute and steady-state assessments, the entire 30-year distribution of estimated daily concentrations in groundwater was incorporated into DEEM-FCID and used in the probabilistic analyses. For steady-state, the daily time series were recalculated using the 21-day rolling averages. In the 21-day rolling average distributions, the first data point is the average of days 1-21, the second data point is the average of days 2-22, the third data point is the average of days 3-23, etc. The estimated daily concentrations were adjusted by a 50x toxicity adjustment factor to account for the relative toxicity of bensulide oxon with respect to parent bensulide, refer to section 5.4.1.

## 5.4 Dietary Risk Assessment

### 5.4.1 Description of Residue Data Used in Dietary Assessment

#### Relative Toxicity of the Oxon

In order to account for the relative toxicity of bensulide oxon with respect to parent bensulide, a CCA study is needed. However, EPA plans to move forward with bensulide human health risk assessment without toxicity data for bensulide's oxon degradate. In lieu of bensulide-specific oxon CCA data, EPA will use an oxon toxicity adjustment factor of 50x in its calculations. This value considers the data derived toxicity adjustment factor EPA has identified among oxon metabolites for other organophosphates, with an additional margin of safety included due to the uncertainty in extrapolating oxon potency data across chemicals.

#### Anticipated Residues

USDA Pesticide Data Program (PDP) monitoring data were incorporated in the dietary assessment. In years 2010 to 2013, USDA PDP analyzed several commodities for residues bensulide and its oxon separately. PDP monitoring data are available for residues of bensulide and its oxon in carrots, carrots baby food, summer squash, cherry tomatoes, and lettuce. PDP monitoring data are only available for parent bensulide for celery, winter squash, hot peppers, onion, canned spinach and frozen spinach. When the oxon analog was not measured, concentration adjustment factors of 1x were used; however, for leafy vegetables a factor of 9x was used since data suggest that residues of the oxon are likely to be higher than those of bensulide (see Appendix E). These factors were used in addition to the previously mentioned 50x toxicity adjustment factor. When the commodity was not analyzed by the USDA PDP or translations were not possible, tolerance level residues were used. Anticipated residues using tolerances are based on the LOQ or 2 times the LOQ (data adjusted due to loss of parent bensulide during storage) of the data acquisition method.

#### **5.4.2 Percent Crop Treated Used in Dietary Assessment**

The following maximum percent crop treated estimates (Updated Screening Level Usage Analysis Report for Bensulide, PC Code 009801; 07/10/2015) were used in the acute and steady-state dietary risk assessment for the following crops that are currently registered for bensulide: broccoli: 25%; Brussels sprouts: 5%; cabbage: 20%; cantaloupes: 40%; cauliflower: 20%; celery: 5%; cucumbers: 5%; honeydews: 30%; lettuce: 40%; onions: 20%; peppers: 10%; pumpkins: 10%; spinach: 10%; squash: 15%; and watermelons: 10%. Percent of crop treated estimates were not provided for carrot, tomato, eggplant, okra and several non-representative crops under the cucurbit, leafy and brassica vegetables; 100% of crop treated were assumed for these crops.

#### **5.4.3 Acute Dietary Risk Assessment**

The acute dietary exposure estimates from food alone are below HED's level of concern (LOC) at the 99.9<sup>th</sup> percentile of exposure for the general population and all population subgroups. The highest exposed population subgroup was children 3-5 years old with an exposure of 0.005016 mg/kg/day occupying 46% of the aPAD. Exposures are above the LOC for drinking water only. For food and drinking water, using the drinking water scenario that provided the highest EDWC (NC Cotton), the dietary exposure estimates were >10,000 of the aPAD at the 95<sup>th</sup>, 99<sup>th</sup> and 99.9<sup>th</sup> percentile of exposure for most population subgroups with All Infants (< 1 year old) having the highest exposure (Table 5.4.6). In addition, using the drinking water scenario (California Avocado) that provided the lowest EDWC, the dietary exposure estimates were >1600% of the aPAD at the 99.9<sup>th</sup> percentile of exposure for the general population and most population subgroups. For Adults 50-99 years old, for which the FQPA SF is 1x, exposures were above the LOC for food and drinking water (NC Cotton and CA Avocado) as well. In summary, acute aggregate (food and drinking water) dietary exposure estimates are above HED's level of concern.

#### 5.4.4 Steady-state Dietary Risk Assessment

The steady-state dietary exposure estimates from food alone are below HED's LOC at the 99.9<sup>th</sup> percentile of exposure for the general population and all population subgroups. The highest exposed population subgroup was children 3-5 years old with an exposure of 0.004779 mg/kg/day occupying 80% of the ssPAD. Exposures are above the LOC for drinking water only. For food and drinking water, using the scenario that provided the highest EDWC, dietary exposure estimates were >10,000 of the ssPAD at the 95<sup>th</sup>, 99<sup>th</sup> and 99.9<sup>th</sup> percentile of exposure for population subgroups with All Infants (< 1 year old) having the highest exposure (Table 5.4.6). In addition, using the drinking water scenario (California Avocado) that provided the lowest EDWC, the dietary exposure estimates were >2900% of the ssPAD at the 99.9<sup>th</sup> percentile of exposure for the general population and all population subgroups. For Adults 50-99 years old, for which the FQPA SF is 1x, exposures were above the LOC for food and drinking water (NC Cotton and CA Avocado) as well. In summary, steady-state aggregate (food and drinking water) dietary exposure estimates are above HED's level of concern.

#### 5.4.5 Cancer Dietary Risk Assessment

Bensulide has been classified as not likely to be carcinogenic in humans via relevant routes of exposure; therefore, a cancer dietary assessment is not needed.

#### 5.4.6 Summary Tables

<b>Table 5.4.6.1. Summary of <u>Acute</u> Dietary (Food Only, and Food and Drinking Water) Exposure and Risk for Bensulide and for Bensulide Oxon (Expressed as Bensulide Equivalents) at the 99.9<sup>th</sup> Percentile.*</b>						
Population Subgroup	Food Only		Food and Water (NC Cotton)		Food and Water (CA Avocado)	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.003459	31	7.200738	>10000	0.259261	2400
All Infants (<1 year old)	0.003299	30	15.584203	<b>&gt;10000</b>	0.617566	<b>5600</b>
Children 1-2 years old	0.004436	40	10.366006	>10000	0.381599	3500
Children 3-5 years old	0.005016	<b>46</b>	6.774460	>10000	0.274069	2500
Children 6-12 years old	0.003835	35	6.321278	>10000	0.214996	2300
Youth 13-19 years old	0.002713	25	4.816789	>10000	0.180075	2000
Adults 20-49 years old	0.002241	20	5.199845	>10000	0.205208	1600
Adults 50-99 years old	0.002124	1.9	4.856943	4400	0.187992	170
Females 13-49 years old	0.002685	24	5.059084	>10000	0.202361	1800

\* The subpopulation with the highest risk estimate is bolded.

**Table 5.4.6.2. Summary of Steady-state Dietary (Food Only, and Food and Drinking Water) Exposure and Risk for Bensulide and for Bensulide Oxon (Expressed as Bensulide Equivalents) at the 99.9<sup>th</sup> Percentile. \***

Population Subgroup	Food Only		Food and Water (NC Cotton)		Food and Water (CA Avocado)	
	Dietary Exposure (mg/kg/day)	% ssPAD	Dietary Exposure (mg/kg/day)	% ssPAD	Dietary Exposure (mg/kg/day)	% ssPAD
General U.S. Population	0.003454	58	7.197920	>10000	0.256468	4300
All Infants (<1 year old)	0.003322	55	15.581721	<b>&gt;10000</b>	0.603403	<b>&gt;10000</b>
Children 1-2 years old	0.004436	74	10.393019	>10000	0.378531	6300
Children 3-5 years old	0.004779	<b>80</b>	6.795017	>10000	0.267948	4500
Children 6-12 years old	0.003836	64	6.315285	>10000	0.212895	3500
Youth 13-19 years old	0.002710	45	4.781498	>10000	0.176266	2900
Adults 20-49 years old	0.002240	37	5.194808	>10000	0.200449	3300
Adults 50-99 years old	0.002121	3.6	4.851935	8100	0.182459	300
Females 13-49 years old	0.002687	45	5.053817	>10000	0.196688	3300

\* The subpopulation with the highest risk estimate is bolded.

## 6.0 Residential (Non-Occupational) Exposure/Risk Characterization

### 6.1 Residential Handler Exposure

HED uses the term “handlers” to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are addressed somewhat differently by HED as homeowners are assumed to complete all elements of an application without use of any protective equipment.

The quantitative exposure/risk assessment developed for residential handlers is based on the following scenarios:

- Mixing/loading/applying liquid and granular formulations dispersed by hand to residential turf/lawns, and
- Mixing/loading/applying liquid and granular formulations with handheld equipment to residential turf/lawns.

#### Residential Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential handler risk assessments. Each assumption and factor is detailed below.

#### *Application Rate:*

Application rates are listed in Table 3.3.

#### *Unit Exposures and Area Treated or Amount Handled:*

Unit exposure values and estimates for area treated or amount handled were taken from HED's 2012 Residential SOPs<sup>5</sup>.

*Exposure Duration:*

Residential handler exposure is assessed as steady-state in duration.

*Body Weight:*

For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female-specific body weight was used to protect for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects (See Section 4.4).

Residential Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate exposure and dose for residential handlers can be found in the 2012 Residential SOPs<sup>6</sup>.

Combining Exposures/Risk Estimates:

A total aggregated risk index (ARI) was used since the LOCs for dermal exposure (1000) and inhalation exposure (3000) are different. The target ARI is 1; therefore, ARIs of less than 1 are risk estimates of concern. The aggregate risk index (ARI) was calculated as follows.

$$\text{Aggregate Risk Index (ARI)} = 1 \div [(\text{Dermal LOC} \div \text{Dermal MOE}) + (\text{Inhalation LOC} \div \text{Inhalation MOE})]$$

Summary of Residential Handler Non-Cancer Exposure and Risk Estimates

A summary of residential handler risk estimates is provided in Table 6.1.1 below. Most residential handler risk estimates are of concern (ARI < 1).

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<sup>5</sup> Available: <http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide>

<sup>6</sup> Available: <http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide>

**Table 6.1.1. Residential Handler Non-cancer Exposure and Risk Estimates for Bensulide.**

Exposure Scenario	Level of Concern	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (mg/lb ai)	Maximum Application Rate <sup>1</sup>	Area Treated or Amount Handled Daily <sup>2</sup>	Dermal		Inhalation		Total
						Dose (mg/kg/day) <sup>3</sup>	MOE <sup>4</sup>	Dose (mg/kg/day) <sup>5</sup>	MOE <sup>6</sup>	ARI <sup>7</sup>
Mixer/Loader/Applicator										
Liquid Concentrate, Handwand, Lawns	1000 for dermal 3000 for inhalation	63	0.018	0.16 lb ai/gal	5 gallons	0.073	<b>82</b>	0.0002	29,000	<b>0.081</b>
Ready-to-use, hose end sprayer, Lawns		6.26	0.034	8.7 lb ai/acre	0.5 acres	0.039	<b>150</b>	0.0021	<b>2,800</b>	<b>0.13</b>
Liquid, Backpack, Lawns		130	0.14	0.16 lb ai/gal	5 gallons	0.15	<b>40</b>	0.0016	3,700	<b>0.039</b>
Granule, Push type rotary spreader, Lawns		0.81	0.0026	12.5 lb ai/acre	0.5 acres	0.0073	<b>820</b>	0.0002	25,000	<b>0.75</b>
Granule, belly grinder, lawns		360	0.039	0.00029 lb ai/ft <sup>2</sup>	1200 ft <sup>2</sup>	0.18	<b>33</b>	0.0002	31,000	<b>0.033</b>
Granule, Spoon, Lawns		6.2	0.087		100 ft <sup>2</sup>	0.00026	23,000	0.000037	160,000	16
Granule, Cup, Lawns		0.11	0.013			0.0000046	1,300,000	0.0000055	1,100,000	290
Granule, Hand dispersal, Lawns		160	0.38			0.0067	<b>890</b>	0.00016	38,000	<b>0.83</b>
Granule, Shaker can, Lawns		0.11	0.013			0.0000046	1,300,000	0.0000055	1,100,000	290

1 Based on registered labels (see Table 3.3).

2 Based on HED's 2012 Residential SOPs (<http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide>).

3 Dermal Dose = Dermal Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre, ft<sup>2</sup> or gal) × Area Treated or Amount Handled (A or ft<sup>2</sup>/day or gallons/day) × Dermal Absorption Factor (10%) ÷ Body Weight (69 kg).

4 Dermal MOE = Dermal NOAEL (6 mg/kg/day) ÷ Dermal Dose (mg/kg/day).

5 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre, ft<sup>2</sup> or gal) × Area Treated or Amount Handled (A or ft<sup>2</sup>/day or gallons/day) ÷ Body Weight (69 kg).

6 Inhalation MOE = Inhalation NOAEL (6 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

7 ARI = Aggregate Risk Index = 1 ÷ [(Dermal LOC ÷ Dermal MOE) + (Inhalation LOC ÷ Inhalation MOE)]

## 6.2 Residential Post-Application Exposure

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with bensulide. The quantitative exposure/risk assessment for residential post-application exposures is based on the following scenarios:

- Dermal exposure from high contact with treated turf (adults and children 1 to < 2 years old),
- Dermal exposure from golfing (adults and youth 11 to < 16 years old and youth 6 to < 11 years old),
- Dermal exposure from mowing treated turf (adults and youth 11 to < 16 years old),
- Incidental ingestion (i.e., hand-to-mouth, object-to-mouth, soil ingestion exposure) from contact with treated turf (children 1 to < 2 years old), and
- Episodic granular ingestion (children 1 to < 2 years old).

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs<sup>7</sup>. While not the only lifestage potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

### Residential Post-application Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor is detailed in the 2012 Residential SOPs<sup>7</sup>.

#### *Application Rate:*

Application rates are listed in Table 3.3.

#### *Body Weight*

For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female-specific body weight was used to protect for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects (See Section 4.4). For children, body weights of 57, 32 and 11 kg was used to assess exposure to children 11 to <16 years, 6 to <11 years, and 1 to <2 years old.

#### *Turf Transferable Residue (TTR) Data:*

##### Liquid Formulations:

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<sup>7</sup> Available: <http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide>

Chemical-specific TTR data are available for bensulide and are summarized in Table 6.2.1 (review: D413875, 10/29/13, A. Rivera-Lupiañez). The study includes TTR data on bensulide and its metabolite, bensulide oxon, that dislodged from turf treated with a liquid formulation containing bensulide at a rate of 12.5 lb ai/A. The product was watered in immediately following the application. Residues were sampled using the modified California Roller technique. First-order dissipation kinetics was assumed in order to generate dissipation curves for bensulide and combined residues of bensulide and bensulide oxon. The summary of statistics includes only post-irrigation measurements as the product labels require the product to be watered in. Due to the differences in the dissipation of bensulide and the oxon, residues of the oxon were adjusted by the toxicity adjustment factor (TAF; oxon residue,  $\mu\text{g}/\text{cm}^2 * 50\text{X TAF}$ ), and total residues (bensulide + adjusted oxon) were used to determine the risk resulting from exposures following bensulide applications. For assessment of residential post-application exposures, the predicted day 0 combined residue ( $0.479 \mu\text{g}/\text{cm}^2$ ) was used in the exposure calculations (see Table 6.2.1 below).

<b>Table 6.2.1. Regression Summary for Turf Treated with BENSUMEC 4LF (MRID 44799001)</b>				
Statistic	Bensulide	Bensulide oxon	Combined residues	Combined Residue with 50x factor for oxon <sup>1</sup>
Actual Application Rate (lb ai/A)	12.6			
Actual Average Residues 8-12 hours after application ( $\mu\text{g}/\text{cm}^2$ ) (post-irrigation )	0.2093	0.0057	0.2144	0.4627
Predicted Day 0 Residues ( $\mu\text{g}/\text{cm}^2$ ) (post-irrigation )	0.201	0.002	0.206	<b>0.479</b>
Slope	-0.27	-0.049	-0.271	-0.303
Half-life (days)	2.6	14.2	2.6	2.3
R <sup>2</sup>	0.897	0.0285	0.8934	0.8123

**Bolded value represents residue value used in post-application exposure calculations.**

<sup>1</sup> Combined residue,  $\mu\text{g}/\text{cm}^2 = [(\text{oxon residue, } \mu\text{g}/\text{cm}^2) * 50\text{X TAF}] + [\text{bensulide residue, } \mu\text{g}/\text{cm}^2]$

#### Solid Formulations:

Chemical-specific TTR data are not available for solid formulations applied to turf; liquid TTR data were used as surrogate. This is considered a health protective approach since, in general, granular formulations tend to result in lower percent transfer from turf than do liquid formulations (e.g., the 2012 Residential SOP turf default percent transfer factor is 1% for liquids and 0.2% for granulars).

#### *Exposure Duration:*

The exposure duration for residential post-application exposures is steady-state. Granule ingestion is considered episodic and thus is an acute duration.

#### Residential Post-application Non-Cancer Exposure and Risk Equations

The algorithms used to estimate residential post-application exposure and dose can be found in the 2012 Residential SOPs<sup>8</sup>.

### Combining Exposure and Risk Estimates

Since dermal and incidental oral exposure routes share a common toxicological endpoint, risk estimates have been combined for those routes. The incidental oral scenarios (i.e., hand-to-mouth and object-to-mouth) should be considered inter-related, and it is likely that they occur interspersed amongst each other across time. Combining these scenarios with the dermal exposure scenario would be overly-conservative because of the conservative nature of each individual assessment. Therefore, the post-application exposure scenarios that were combined for children 1 < 2 years old are the dermal and hand-to-mouth scenarios. This combination should be considered a protective estimate of children's exposure.

### Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

A summary of the residential post-application exposure and risk estimates for bensulide and its oxon is in Tables 6.2.2 (for liquid formulations) and 6.2.3 (for solid formulations) below. Risk estimates are of concern (MOEs < 1000) for dermal exposure for adults and children conducting high exposure activities on treated turf; for dermal exposure for adults and youths golfing; for hand-to-mouth exposure for children on treated turf; and for episodic granule ingestion exposure.

**Table 6.2.2. Residential Post-Application Non-Cancer Exposure and Risk Estimates for Bensulide + Oxon (Liquid Formulations).**

Lifestage	Post-application Exposure Scenario		Application Rate <sup>1</sup>	Dose (mg/kg/day) <sup>2</sup>	MOEs (LOC = 1000) <sup>3</sup>	Combined Routes (X indicates included in Combined MOE)	Combined MOEs (LOC = 1000) <sup>4</sup>
	Use Site	Route of Exposure					
Adult	Lawns/ Turf	Dermal – Turf	12.5 lb ai/A	0.187	32	NA	
		Dermal - Mowing		0.0038	1,600		
		Dermal – Golfing		0.0147	410		
Youth (11 to < 16 years)		Dermal- Mowing		0.00378	1,600		
		Dermal – Golfing		0.0148	410		
Youth (6 to < 11 years)		Dermal- Golfing		0.0174	350		
Child (1 to < 2 years)		Dermal - Turf		0.32	19	X	16
		Hand-to-Mouth		0.0656	91	X	
		Object-to-Mouth		0.00199	3,000	NA	
		Soil Ingestion		0.00042	14,000	NA	

1 Based on registered labels (see Table 3.3). Predicted Day 0 combined (bensulide + adjusted oxon) residue value (0.479 ug/cm<sup>2</sup>; from MRID 44799001) used in calculations.

2 Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (<http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide>).

3 MOE = Dermal and Incidental Oral POD (6 mg/kg/day) ÷ Dose (mg/kg/day).

4 Combined MOE = 1 ÷ (1/dermal MOE) + (1/incidental oral MOE), where applicable.

<sup>8</sup> Available: <http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide>

**Table 6.2.3. Residential Post-Application Non-Cancer Exposure and Risk Estimates for Bensulide + Oxon (Solid Formulations).**

Lifestage	Post-application Exposure Scenario		Application Rate <sup>1</sup>	Dose (mg/kg/day) <sup>2</sup>	MOEs (LOC = 1000) <sup>3</sup>	Combined Routes (X indicates included in Combined MOE)	Combined MOEs (LOC = 1000) <sup>4</sup>
	Use Site	Route of Exposure					
Adult	Lawns/ Turf	Dermal – Turf	12.5 lb ai/A	0.2082	<b>29</b>	NA	
		Dermal - Mowing		0.0038	1,600		
		Dermal – Golfing		16 lb ai/A	0.0188		
Youth (11 to < 16 years)		Dermal- Mowing	12.5 lb ai/A	0.00378	1,600		
Youth (6 to < 11 years)		Dermal – Golfing	16 lb ai/A	0.0189	<b>320</b>		
		Dermal- Golfing		0.0222	<b>270</b>		
Child (1 to < 2 years)		Dermal - Turf	12.5 lb ai/A	0.3527	<b>17</b>	X	<b>16</b>
		Hand-to-Mouth		0.0325	<b>180</b>	X	
		Object-to-Mouth		0.00199	3,000	NA	
		Soil Ingestion		0.00042	14,000		
		Episodic Granule Ingestion (12.5% ai)		3.41	<b>3.2</b>		

1 Based on registered labels (See Table 3.3). Predicted Day 0 combined (bensulide + adjusted oxon) residue value (0.479 ug/cm<sup>2</sup>; from MRID 44799001) used in calculations.

2 Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (<http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide>).

3 MOE = Dermal and Incidental Oral POD (6 mg/kg/day) ÷ Dose (mg/kg/day).

4 Combined MOE = 1 ÷ (1/dermal MOE) + (1/incidental oral MOE), where applicable.

## 6.4 Residential Risk Estimates for Use in Aggregate Assessment

As the residential turf scenarios are risks of concern, there are no residential risk estimates recommended for steady state aggregate assessment.

## 6.5 Residential Bystander Post-application Inhalation Exposure

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (<http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037>). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (<http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219>). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for bensulide.

The California Department of Pesticide Regulation (DPR) has released a draft report on its air monitoring network for public comment. In 2011, DPR established a monitoring network to sample ambient air for multiple pesticides in three communities on a regular basis. The draft report of results for the monitoring in 2014 is available at [http://www.cdpr.ca.gov/docs/emon/airinit/air\\_network\\_results.htm](http://www.cdpr.ca.gov/docs/emon/airinit/air_network_results.htm). In the draft Air Monitoring Network Results for 2014 report, there were 0 detections of bensulide of 157 samples. Furthermore, in the 2012 and 2013 reports, there were 0 detections of bensulide. In the 2011

report, there were 5 detects of bensulide of 142 samples; all detects were below the quantitation limit.

## 6.6 Non-Occupational Spray Drift Exposure and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (e.g., children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling onto 50 feet wide lawns coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.<sup>9</sup> Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to <2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female-specific body weight was used to protect for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects (See Section 4.4).

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of bensulide. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDrift® (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures For Residential Risk Assessment (SOPs)*.

For bensulide, chemical-specific turf transferable residue (TTR) data are available and were used for assessment of spray drift risks. See Section 6.2 for a description of the TTR data. The data

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<sup>9</sup> This approach is consistent with the requirements of the EPA's Worker Protection Standard.

include measurements on bensulide and the oxon. For assessment of exposures resulting from spray drift, the predicted day 0 combined (bensulide + adjusted oxon) residue value (0.479 ug/cm<sup>2</sup>) was adjusted for differences in application rate between the study and the registered agricultural uses, and the adjusted residue value was used in the exposure calculations.

A screening approach was developed based on the use of the AgDrift<sup>®</sup> model in situations where specific label guidance that defines application parameters is not available.<sup>10</sup> AgDrift<sup>®</sup> is appropriate for use only when applications are made by aircraft, airblast orchard sprayers, and groundboom sprayers. When AgDrift<sup>®</sup> was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. These screening options are consistent with how spray drift is considered in a number of ecological risk assessments and in the process used to develop drinking water concentrations used for risk assessment. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed). Table 6.6.1 provides the screening level drift related risk estimates. In many cases, risk estimates are of concern when the screening level estimates for spray drift are used as the basis for the analysis. In order to account for this issue and to provide additional risk management options, additional spray drift deposition fractions were also considered. These drift estimates represent plausible options for pesticide labels.

#### Combined Risk Estimates from Lawn Deposition Adjacent to Applications

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Bensulide is registered in both liquid and granular formulation end-use products. Granular formulations, applied as solid materials and no liquid spray, have different drift patterns than liquid sprays, and as such, need to be considered in a separate analysis. However, from a human health perspective, off-site movement of granular products would result in lower risk estimates than those for liquid products (e.g., less drift occurs and there is less exposure uptake for granules). In most cases, pesticides also have liquid end-use products and an analysis for them would be protective of potential risks from granular drift; thus, granular products are not assessed.

Bensulide is registered on vegetable crops and golf courses, and can be applied via groundboom equipment at a maximum single application rate of 6 lb ai/A for vegetable crops (9 lb ai/A on SLN labels) and 12.5 lb ai/acre for golf courses. The recommended drift scenario screening level options are listed below:

- Groundboom applications are based on the AgDrift<sup>®</sup> option for high boom height and using very fine to fine spray type using the 90<sup>th</sup> percentile results.

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<sup>10</sup> <http://www.agdrift.com/>

In addition to the screening level spray drift scenarios described above, additional results are provided which represent viable drift reduction technologies (DRTs) that represent potential risk management options. In particular, different spray qualities have been considered as well as the impact of other application conditions (e.g., boom height and crop canopy conditions).

Dermal risk estimates were calculated for adults. Dermal and incidental oral risk estimates for children (1 to <2 years old) were combined because the toxicity endpoint for each route of exposure is the same (RBC AChE inhibition). The total applicable LOC is 1000, so MOEs <1000 represent risk estimates of concern.

Risk estimates related to spray drift are of concern at various distances from the edge of the field for adults and children (1 to <2 years) depending on the spray drift scenario. Adult and children risk estimates are summarized in Table 6.6.1. For adults, the screening level scenario indicates the LOC is exceeded at a distance of less than 25 feet for applications to vegetables and less than 75 feet for applications to golf courses. For children, the screening level scenario indicates the LOC is exceeded at a distance of less than 75 feet for applications to vegetables and 150 feet for applications to golf courses. Drift reduction technologies, such as using coarser sprays and lowering boom height for groundboom sprayers, reduces risk concerns; however, there are still risk estimates of concern at the field edge for some scenarios.

Table 6.6.1. Spray Drift Risk Estimate Summary for Bensulide.														
Crop / Application Type	Spray Type/ Nozzle Configuration	Application Rate (lb ai/A)	Estimated TTR (ug/cm²)	MOE at Different Distances from Edge of Field LOC = 1000										
				At Edge	10 Feet	25 Feet	50 Feet	75 Feet	100 Feet	125 feet	150 feet	200 feet	250 feet	300 feet
Adults (Dermal Exposure Only); Vegetable Crops (6 lb ai/acre)														
Vegetable / Groundboom	Screening Level High Boom Very fine to Fine	6	0.2299	360	720	1,200	1,900	2,700	3,300	3,900	4,800	6,100	8,300	9,500
	Low Boom Very fine to Fine			780	2,100	3,300	5,100	6,700	8,300	9,500	11,000	13,000	17,000	22,000
	High Boom Fine to Medium / Coarse			1,400	3,500	5,100	7,400	9,500	11,000	13,000	13,000	17,000	22,000	22,000
	Low Boom Fine to Medium / Coarse			2,000	5,600	8,300	11,000	13,000	17,000	22,000	22,000	33,000	33,000	33,000
Adults (Dermal Exposure Only); Vegetable Crops (SLN rate of 9 lb ai/acre)														
Vegetable / Groundboom	Screening Level High Boom Very fine to Fine	9	0.345	240	480	790	1,300	1,800	2,200	2,600	3,200	4,000	5,600	6,400
	Low Boom Very fine to Fine			520	1,400	2,200	3,400	4,400	5,600	6,400	7,400	8,900	11,000	15,000
	High Boom Fine to Medium / Coarse			910	2,300	3,400	4,900	6,400	7,400	8,900	8,900	11,000	15,000	15,000
	Low Boom Fine to Medium / Coarse			1,300	3,700	5,600	7,400	8,900	11,000	15,000	15,000	22,000	22,000	22,000
Adults (Dermal Exposure Only); Golf Courses														
Golf Course/ Groundboom	Screening Level High Boom Very fine to Fine	12.5	0.479	170	340	570	910	1,300	1,600	1,900	2,300	2,900	4,000	4,600
	Low Boom Very fine to Fine			380	1,000	1,600	2,500	3,200	4,000	4,600	5,300	6,400	8,000	11,000
	High Boom Fine to Medium / Coarse			650	1,700	2,500	3,600	4,600	5,300	6,400	6,400	8,000	11,000	11,000
	Low Boom Fine to Medium / Coarse			970	2,700	4,000	5,300	6,400	8,000	11,000	11,000	16,000	16,000	16,000
Children (1 to < 2 years old) (Dermal and Incidental Oral Exposure); Vegetable Crops (6 lb ai/acre)														

Table 6.6.1. Spray Drift Risk Estimate Summary for Bensulide.														
Crop / Application Type	Spray Type/ Nozzle Configuration	Application Rate (lb ai/A)	Estimated TTR (ug/cm <sup>2</sup> )	MOE at Different Distances from Edge of Field LOC = 1000										
				At Edge	10 Feet	25 Feet	50 Feet	75 Feet	100 Feet	125 feet	150 feet	200 feet	250 feet	300 feet
Vegetable / Groundboom	Screening Level High Boom Very fine to Fine	6	0.2299	170	350	580	930	1,300	1,600	1,900	2,300	2,900	4,100	4,600
	Low Boom Very fine to Fine			380	1,000	1,600	2,500	3,200	4,100	4,600	5,400	6,500	8,100	11,000
	High Boom Fine to Medium/Coarse			660	1,700	2,500	3,600	4,600	5,400	6,500	6,500	8,100	11,000	11,000
	Low Boom Fine to Medium/Coarse			980	2,700	4,100	5,400	6,500	8,100	11,000	11,000	16,000	16,000	16,000
Children (1 to < 2 years old) (Dermal and Incidental Oral Exposure); Vegetable Crops (SLN rate of 9 lb ai/acre)														
Vegetable / Groundboom	Screening Level High Boom Very fine to Fine	9		120	230	390	620	860	1,100	1,300	1,500	2,000	2,700	3,100
	Low Boom Very fine to Fine			250	680	1,100	1,700	2,200	2,700	3,100	3,600	4,300	5,400	7,200
	High Boom Fine to Medium/Coarse			440	1,100	1,700	2,400	3,100	3,600	4,300	4,300	5,400	7,200	7,200
	Low Boom Fine to Medium/Coarse			650	1,800	2,700	3,600	4,300	5,400	7,200	7,200	11,000	11,000	11,000
Children (1 to < 2 years old) (Dermal and Incidental Oral Exposure); Golf Courses														
Golf Course/ Groundboom	Screening Level High Boom Very fine to Fine	12.5	0.479	83	170	280	440	620	780	920	1,100	1,400	1,900	2,200
	Low Boom Very fine to Fine			180	490	780	1,200	1,600	1,900	2,200	2,600	3,100	3,900	5,200
	High Boom Fine to Medium/Coarse			320	820	1,200	1,700	2,200	2,600	3,100	3,100	3,900	5,200	5,200
	Low Boom Fine to Medium/Coarse			470	1,300	1,900	2,600	3,100	3,900	5,200	5,200	7,800	7,800	7,800

**Bolded values are below the LOC of 1000.**

## 7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

### 7.1 Acute Aggregate Risk

The acute aggregate risk assessment combines oral exposure through food and drinking water which is represented by the acute dietary assessment, refer to Section 5.4.3.

### 7.2 Steady-state Aggregate Risk

The steady-state aggregate assessment combines steady-state dietary (food and water) and residential exposures. Because there are risks of concern associated with dietary and residential exposure, an aggregate risk assessment was not conducted.

### 7.3 Cancer Aggregate Risk

Bensulide has been classified as not likely to be carcinogenic in humans via relevant routes of exposure; therefore, a cancer aggregate assessment is not needed.

## 8.0 Cumulative Exposure/Risk Characterization

OPs, like bensulide, share the ability to inhibit AChE through phosphorylation of the serine residue on the enzyme leading to accumulation of acetylcholine and ultimately cholinergic neurotoxicity. This shared MOA/AOP is the basis for the OP common mechanism grouping per OPP's *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999). The 2002 and 2006 CRAs used brain AChE inhibition in female rats as the source of dose response data for the relative potency factors and PODs for each OP, including bensulide. Prior to the completion of Registration Review, OPP will update the OP CRA on AChE inhibition to incorporate new toxicity and exposure information available since 2006.

As described in Section 4.4, OPP has retained the FQPA Safety Factor for OPs, including bensulide, due to uncertainties associated with neurodevelopmental effects in children and exposure to OPs. There is a lack of an established MOA/AOP for the neurodevelopment outcomes which precludes the Agency from formally establishing a common mechanism group per the *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999) based on that outcome. Moreover, the lack of a recognized MOA/AOP and other uncertainties with exposure assessment in the epidemiology studies prevent the Agency from establishing a causal relationship between OP exposure and

neurodevelopmental outcomes. The Agency will continue to evaluate the epidemiology studies associated with neurodevelopmental outcomes and OP exposure prior to the release of the revised DRA. During this period, the Agency will determine whether or not it is appropriate to apply the draft guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* for the neurodevelopment outcomes.

## 9.0 Occupational Exposure/Risk Characterization

Exposure to bensulide is assessed for handler scenarios; exposure to bensulide and bensulide oxon was assessed for post-application scenarios.

### 9.1 Steady-State Handler Risk

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications, and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Mixing/loading granules for tractor application,
- Mixing/loading liquids for chemigation and groundboom application,
- Applying granules via tractor,
- Applying sprays via groundboom equipment,
- Mixing/loading/applying liquids via handgun equipment, and
- Mixing/loading/applying granules via rotary spreader.

#### Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

##### *Application Rate:*

A summary of application rates is provided in Table 3.3.

*Unit Exposures:* It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data) and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this

assessment, known as “unit exposures”, are outlined in the “Occupational Pesticide Handler Unit Exposure Surrogate Reference Table<sup>11</sup>”, which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website<sup>12</sup>.

*Area Treated or Amount Handled:*

Based on ExpoSAC Policy 9.1, the area treated or amount handled is assumed to be:

- 40 acres for tractor or groundboom applications to golf courses,
- 350 acres for chemigation applications,
- 80 acres for groundboom applications to typical field crops (vegetables),
- 1000 gallons for handgun applications to field crops (vegetables), and
- 5 acres for handgun/rotary spreader applications to golf courses.

*Exposure Duration:*

For bensulide, based on the proposed use, steady-state exposure is expected.

*Mitigation/Personal Protective Equipment:* Estimates of dermal and inhalation exposure were calculated for various levels of personal protective equipment (PPE). Results are presented for the label-required PPE, and also with various levels of additional PPE, as necessary. A summary of PPE requirements is listed in Table 3.3.

*Body Weight:* For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female-specific body weight was used to protect for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects (See Section 4.4).

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in the occupational and residential exposure (ORE) memo for bensulide (D428877, A. Gavalek and K. Lowe, 03/03/2016).

Combining Exposures/Risk Estimates:

A total aggregated risk index (ARI) was used since the LOC values for dermal exposure (1000) and inhalation exposure (3000) are different. The target ARI is 1; therefore, ARIs of less than 1 are risk estimates of concern. The aggregate risk index (ARI) was calculated as follows.

$$\text{Aggregate Risk Index (ARI)} = 1 \div [(\text{Dermal LOC} \div \text{Dermal MOE}) + (\text{Inhalation LOC} \div \text{Inhalation MOE})]$$

<sup>11</sup> Available: <http://www2.epa.gov/sites/production/files/2015-09/documents/handler-exposure-table-2015.pdf>

<sup>12</sup> Available: <http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data>

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

A summary of occupational handler risk estimates for bensulide with the label-required PPE is provided in Table 9.1.1 below. With the label-required PPE, all handler risk estimates (combined dermal and inhalation) are of concern ( $ARI < 1$ ). A summary of handler risk estimates with additional PPE/ engineering controls to mitigate risks is provided in Table 9.1.2; most handler risk estimates are still of concern with the maximum PPE/ engineering controls.

Table 9.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Bensulide (with label-required PPE).										
Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai) <sup>1</sup>	Inhalation Unit Exposure (µg/lb ai) <sup>1</sup>	Maximum Application Rate <sup>2</sup>	Area Treated or Amount Handled Daily <sup>3</sup>	Dermal		Inhalation		Total
						Dose (mg/kg/day) <sup>4</sup>	MOE <sup>5</sup> (LOC = 1000)	Dose (mg/kg/day) <sup>6</sup>	MOE <sup>7</sup> (LOC = 3000)	ARI <sup>8</sup>
Mixer/Loader										
M/L, Granule, Tractor Application	Golf Course	DL/G: 3.4	PF 5: 0.34	16 lb ai/A	40 A	0.00316	1,900	0.00316	1,900	0.48
M/L, Liquid, Chemigation	Cucurbit/ Brassica/ Fruiting/ Dry bulb Vegetables	SL/ G: 37.6	PF 5: 0.0438	6 lb ai/ A	350 A	0.114	53	0.00133	4,500	0.051
	SLN Vegetables			9 lb ai/A		0.171	35	0.002	3,000	0.034
M/L, Liquid, Groundboom Application	Golf Course			12.5 lb ai/A	40 A	0.0272	220	0.000317	19,000	0.21
	Cucurbit/ Brassica/ Fruiting/ Dry bulb Vegetables			6 lb ai/A	80 A	0.0261	230	0.000304	20,000	0.22
	SLN Vegetables			9 lb ai/A		0.0393	150	0.000457	13,000	0.14
Applicator										
Applying Sprays via Groundboom Equipment	Golf Course	SL/G: 16.1	PF 5: 0.068	12.5 lb ai/A	40 A	0.0117	510	0.000493	12,000	0.45
	Cucurbit/ Brassica/ Fruiting/ Dry bulb Vegetables			6 lb ai/A	80 A	0.0112	540	0.000472	13,000	0.48
	SLN Vegetables			9 lb ai/A		0.0168	360	0.00071	8,500	0.32
Applying Granule via Tractor	Golf Course	SL/G: 7.2	PF 5: 0.24	16 lb ai/A	40 A	0.00668	900	0.00223	2,700	0.45
Mixer/Loader/Applicator										
M/L/A, Liquid, Handgun	Golf Course/ Lawn	SL/ G: 880	PF 5: 0.38	12.5 lb ai/A	5 A	0.0797	75	0.000345	17,000	0.074
	Field Crop	SL/G: 390	PF 5: 0.78	0.16 lb ai/gal	1000 gal	0.0904	66	0.00181	3,300	0.062
L/A, Granule, Rotary Spreader	Lawn	DL/G: 130	PF 5: 2	12.5 lb ai/A	5 A	0.0118	510	0.00181	3,300	0.35
	Golf Course			16 lb ai/A		0.0151	400	0.00232	2,600	0.27

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2013); Level of mitigation: SL/G = Single layer clothing and gloves; DL/G = Double layer clothing and gloves; PF 5 = respirator with protection factor of 5; PF 10 = respirator with protection factor of 10; EC = engineering controls.

2 Based on registered labels (see Table 3.3).

3 Exposure Science Advisory Council Policy #9.1.

4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) × DAF (10%) ÷ BW (69 kg).

5 Dermal MOE = Dermal NOAEL (6 mg/kg/day) ÷ Dermal Dose (mg/kg/day).

6 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (69 kg).

7 Inhalation MOE = Inhalation NOAEL (6 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

8 ARI = Aggregate Risk Index = 1 ÷ [(Dermal LOC ÷ Dermal MOE) + (Inhalation LOC ÷ Inhalation MOE)].

**Table 8.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Bensulide (with additional level of PPE).**

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai) <sup>1</sup>	Inhalation Unit Exposure (µg/lb ai) <sup>1</sup>	Maximum Application Rate <sup>2</sup>	Area Treated or Amount Handled Daily <sup>3</sup>	SL/G + PF 5	DL/G + PF 5	SL/G + PF 10	DL/G + PF 10	EC
						ARI <sup>4</sup>				
Mixer/Loader										
M/L, Granule, Tractor Application	Golf Course	SL/G: 6.9 DL/G: 3.4 EC: 8.6	PF 5: 0.34 PF 10: 0.17 EC: 0.083	16 lb ai/A	40 A	0.38	0.48 (current PPE)	0.54	0.76	0.58
M/L, Liquid, Chemigation	Cucurbit/ Brassica/ Fruiting/ Dry bulb Vegetables	SL/ G: 37.6 DL/ G: 29.1 EC: 8.6	PF 5: 0.0438 PF 10: 0.0219 EC: 0.083	6 lb ai/ A	350 A	0.051 (current PPE)	0.065	0.052	0.066	0.18
	SLN Vegetable			9 lb ai/A		0.034 (current PPE)	0.043	0.034	0.044	0.12
M/L, Liquid, Groundboom Application	Golf Course			12.5 lb ai/A	40 A	0.21 (current PPE)	0.27	0.22	0.27	0.75
	Cucurbit/ Brassica/ Fruiting/ Dry bulb Vegetables			6 lb ai/A	80 A	0.22 (current PPE)	0.29	0.23	0.29	0.77
	SLN Vegetables			9 lb ai/A		0.14 (current PPE)	0.19	0.15	0.2	0.52
Applicator										
Applying Sprays via Groundboom Equipment	Golf Course	SL/G: 16.1 DL/ G: 12.6 EC: 5.1	PF 5: 0.068 PF 10: 0.034 EC: 0.043	12.5 lb ai/A	40 A	0.45 (current PPE)	0.57	0.48	0.61	1.3
	Cucurbit/ Brassica/ Fruiting/ Dry bulb Vegetables			6 lb ai/A	200 A	0.48 (current PPE)	0.59	0.51	0.63	1.4
	SLN Vegetables			9 lb ai/A		0.32 (current PPE)	0.4	0.34	0.43	0.88
Applying Granule via Tractor	Golf Course	SL/G: 7.2 DL/ G: 4.2 EC: 2	PF 5: 0.24 PF 10: 0.12 EC: 0.22	16 lb ai/A	40 A	0.45 (current PPE)	0.56	0.6	0.82	0.74
Mixer/Loader/Applicator										
M/L/A, Liquid, Handgun	Golf Course/ Lawn	SL/ G: 880 DL/G: 450	PF 5: 0.38 PF 10: 0.19	12.5 lb ai/A	5 A	0.074 (current PPE)	0.15	0.075	0.15	NA
	Field Crop	SL/G: 390 DL/G: 290	PF 5: 0.78 PF 10: 0.39	0.16 lb ai/gal	1000 gal	0.062 (current PPE)	0.082	0.064	0.086	NA
L/A, Granule, Rotary Spreader	Lawn	SL/G: 240 DL/G: 130	PF 5: 2 PF 10: 1	12.5 lb ai/A	5 A	0.22	0.35 (current PPE)	0.25	0.41	NA
	Golf Course			16 lb ai/A		0.18	0.27 (current PPE)	0.2	0.33	NA

<sup>1</sup> Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2013); Level of mitigation: SL/G = Single layer clothing and gloves; DL/G = Double layer clothing and gloves; PF 5 = respirator with protection factor of 5; PF 10 = respirator with protection factor of 10; EC = engineering controls.

2 Based on registered labels (see Table 3.3).

3 Exposure Science Advisory Council Policy #9.1.

4  $ARI = \text{Aggregate Risk Index} = 1 \div [(\text{Dermal LOC} \div \text{Dermal MOE}) + (\text{Inhalation LOC} \div \text{Inhalation MOE})]$ .

## 9.2 Steady-State Post-Application Risk

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

### 9.2.1 Dermal Post-Application Risk

Bensulide is registered for use on golf course turf and on vegetable crops. A dermal post-application assessment has been conducted for the golf course turf use. However, since bensulide is applied to vegetables as a preplant or preemergence application only, occupational post-application dermal exposures are not anticipated for these uses. There is a low potential for occupational post-application exposure when pre-emergent herbicides are used. Bensulide is applied to the soil directly and is soil incorporated well before the crops are mature. The timing of the application of bensulide can greatly reduce the potential for post-application exposure. Minimal exposure during harvesting or any other late season activities is expected since bensulide is applied pre-emergent. Therefore, HED does not require a post-application occupational exposure assessment (HED Exposure Science Advisory Council Policy No. 008).

#### Occupational Post-application Dermal Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational post-application risk assessments for the golf course use. Each assumption and factor is detailed below on an individual basis.

##### *Exposure Duration:*

For bensulide, an exposure profile consistent with steady-state exposure is expected.

*Transfer Coefficients:* It is the policy of HED to use the best available data to assess post-application exposure. Sources of generic post-application data, used as surrogate data in the absence of chemical-specific data, are derived from ARTF exposure monitoring studies, and, as proprietary data, are subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting post-application exposure that are used in this assessment, known as "transfer coefficients", are presented in the ExpoSAC Policy 3<sup>13</sup> which, along with additional information about the ARTF data, can be found at the Agency website<sup>14</sup>. Table 9.2.1.1 provides a summary of the anticipated post-application activities and associated transfer coefficients for the proposed crops/use sites.

<sup>13</sup> Available: <http://www2.epa.gov/sites/production/files/2015-08/documents/exposac-policy-3-march2013.pdf>

<sup>14</sup> Available: <http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure>

<b>Table 9.2.1.1. Anticipated Post-Application Activities and Dermal Transfer Coefficients.</b>					
<b>Proposed Crops</b>	<b>Policy Crop Group Category</b>	<b>Crop Height</b>	<b>Foliage Density</b>	<b>Transfer Coefficients (cm<sup>2</sup>/hr)</b>	<b>Activities</b>
Golf Course	Turf	Low	Full	3700	Maintenance

*Application Rate:*

Application rates are listed in Table 3.3.

*Exposure Time:* The average occupational workday is assumed to be 8 hours.

*Turf Transferable Residues:* Chemical-specific TTR data are available for the liquid formulation of bensulide. See Section 6.2 for a description of the TTR data. The data include measurements on bensulide and the oxon. Due to the differences in the dissipation of bensulide and the oxon, residues of the oxon were adjusted by the toxicity adjustment factor (TAF; oxon residue, ug/cm<sup>2</sup> \* 50X TAF), and total residues (bensulide + adjusted oxon) were used to determine the risk resulting from exposures following bensulide applications. Since no data are available for the granular formulation, the liquid formulation residue data were used as a surrogate. As noted above, this is considered a health protective approach since, in general, granular formulations tend to result in lower percent transfer from turf than do liquid formulations (e.g., the 2012 Residential SOP turf default percent transfer factor is 1% for liquids and 0.2% for granulars).

*Body Weight:* For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female-specific body weight was used to protect for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects (See Section 4.4).

Occupational Post-application Non-Cancer Dermal Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational post-application workers can be found in the occupational and residential exposure (ORE) memo for bensulide (D428877, A. Gavalek and K. Lowe, 03/03/2016).

Occupational Post-application Non-Cancer Dermal Risk Estimates

Occupational post-application risks were estimated for workers; risk estimates were of concern until 5 days after treatment (DAT 5). See tables 9.2.1.2 (for liquid formulations) and 9.2.1.3 (for granular formulations) below for a summary of the occupational post-application risk estimates.

**Table 9.2.1.2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Bensulide + Oxon (with 50X TAF) (Liquid Formulations).**

Crop/Site	Activities	Transfer Coefficient (cm <sup>2</sup> /hr)	DAT	TTR <sup>1</sup>	Dermal Dose (mg/kg/day) <sup>2</sup>	MOE (LOC = 1000) <sup>3</sup>
Golf Course	Maintenance	3700	0	0.475	0.0204	<b>290</b>
			1	0.351	0.0151	<b>400</b>
			2	0.259	0.0111	<b>540</b>
			3	0.192	0.0082	<b>730</b>
			4	0.141	0.0061	<b>990</b>
			5	0.105	0.00448	<b>1,300</b>

1 TTR = Data from MRID 44799001. Total TTR, ug/cm<sup>2</sup> = [ (oxon residue, ug/cm<sup>2</sup>) \* 50 X TAF] + [bensulide residue, ug/cm<sup>2</sup>].

2 Daily Dermal Dose = [DFR (ug/cm<sup>2</sup>) × Transfer Coefficient × 0.001 mg/ug × 8 hrs/day × dermal absorption (10%)] ÷ BW (69 kg).

3 MOE = POD (6 mg/kg/day) / Daily Dermal Dose.

**Table 9.2.1.3. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Bensulide + Oxon (with 50X TAF) (Solid Formulations).**

Crop/Site	Activities	Transfer Coefficient (cm <sup>2</sup> /hr)	DAT	TTR <sup>1</sup>	Dermal Dose (mg/kg/day) <sup>2</sup>	MOE (LOC = 1000) <sup>3</sup>
Golf Course	Maintenance	3700	0	0.6083	0.026097	<b>230</b>
			1	0.4493	0.019276	<b>310</b>
			2	0.3319	0.014238	<b>420</b>
			3	0.2452	0.010517	<b>570</b>
			4	0.181	0.00777	<b>770</b>
			5	0.134	0.00574	<b>1,000</b>

1 TTR = Default assumption that 0.2% of application rate available as TTR on day 0. Dissipation rate and oxon conversion data from MRID 44799001. Total TTR, ug/cm<sup>2</sup> = [ (oxon residue, ug/cm<sup>2</sup>) \* 50 X TAF] + [bensulide residue, ug/cm<sup>2</sup>].

2 Daily Dermal Dose = [DFR (ug/cm<sup>2</sup>) × Transfer Coefficient × 0.001 mg/ug × 8 hrs/day × dermal absorption (10%)] ÷ BW (69 kg).

3 MOE = POD (6 mg/kg/day) / Daily Dermal Dose.

### Restricted Entry Interval

Bensulide is classified as Toxicity Category III via the dermal route, Toxicity Category IV for dermal irritation, and Toxicity Category III for eye irritation. It is not a skin sensitizer. Under 40 CFR 156.208 (c) (2), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. However, steady-state post-application risk estimates were a concern up to Day 5 for golf course maintenance activities. Therefore, HED is recommending that the REI for golf courses be revised on the label to address those concerns.

## **9.2.2 Inhalation Post-Application Risk**

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010

(<http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037>). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (<http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219>). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for bensulide.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments.

## 10.0 Public Health and Pesticide Epidemiology Data

Adapted from: S. Recore, D428879, 08/10/2015

IDS records incidents resulting in higher severity outcomes in more detail, in a module called the Main IDS module. This system stores incident data for death, major and moderate incidents, and it includes more details about the location, date and nature of the incident. Main IDS incidents involving only one pesticide are considered to provide more certain information about the potential effects of exposure from the pesticide. The less severe human incidents (minor, unknown, or no effects outcomes) are reported by registrants as counts called aggregate summaries and are recorded in a separate module called Aggregate IDS. The SENSOR-Pesticides database covers 11 states from 1998-2010, although reporting varies from state to state. Cases of pesticide-related illnesses are ascertained from a variety of sources. Although both occupational and non-occupational incidents are included in the database, SENSOR-Pesticides focuses on occupational pesticide incidents, and is of particular value in providing that information. For this evaluation, both the IDS and SENSOR database were consulted for pesticide incident data on the active ingredient bensulide (PC Code: 009801). In addition, we sought information from the Agricultural Health Study (AHS); however, bensulide is not included in the AHS.

Bensulide was previously reviewed in 1998 (J. Blondell and M. Spann, 2/9/1998, D239353). At the time, there were two incidents reported for bensulide in IDS from 1992 – February 1998. Upon review of these incidents, no recommendations were made and it was concluded that, “Very few illness cases have been reported due to bensulide and none have been confirmed.” The current IDS analysis from January 1, 2010 through August 25, 2015, shows 2 moderate severity incident reported involving bensulide in Main IDS and 5 minor severity incidents reported to Aggregate IDS. The query of SENSOR-Pesticides 1998-2011 identified a total of 38 cases involving (pc code 009801). Of these 38 cases, 17 cases, stemming from seven events, involve a single ai and were reviewed further. Fourteen cases were low in severity and three cases were moderate in severity. Sixteen cases were occupational exposure. A total of 14 of the single ai cases reports were caused by two spray drift events.<sup>i</sup>

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<sup>i</sup> SENSOR-Pesticides defines drift as “off-target movement of pesticide” which includes cases of volatilization.

**Conclusion:** Based on the low frequency of incidents involving bensulide reported to both IDS and SENSOR-Pesticides, there does not appear to be a concern at this time. The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be conducted.

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## Appendix A. Toxicology Profile and Executive Summaries

### A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food use for bensulide are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Study	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity .....	yes	yes
870.1200 Acute Dermal Toxicity .....	yes	yes
870.1300 Acute Inhalation Toxicity .....	yes	yes
870.2400 Acute Eye Irritation .....	yes	yes
870.2500 Acute Dermal Irritation .....	yes	yes
870.2600 Skin Sensitization .....	yes	yes
870.3100 90-Day Oral Toxicity in Rodents .....	yes	yes
870.3150 90-Day Oral Toxicity in Non-rodents.....	yes	yes
870.3200 21/28-Day Dermal Toxicity.....	yes	yes
870.3250 90-Day Dermal Toxicity.....	no	-
870.3465 90-Day Inhalation Toxicity .....	yes	<b>no</b>
870.3700a Prenatal Developmental Toxicity in Rodents .....	yes	yes
870.3700b Prenatal Developmental Toxicity in Non-rodents .....	yes	yes
870.3800 Reproduction and Fertility Effects.....	yes	yes
870.4100a Chronic Toxicity in Rodents .....	yes	yes
870.4100b Chronic Toxicity in Non-rodents.....	yes	yes
870.4200a Carcinogenicity in Rats.....	yes	yes
870.4200b Carcinogenicity in Mice .....	yes	yes
870.5100 Mutagenicity—Bacterial Reverse Mutation Test .....	yes	yes
870.5300 Mutagenicity—Mammalian Cell Gene Mutation Test ..	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations...	yes	yes
870.5385 Mutagenicity—Mammalian Bone Marrow Chromosomal Aberration Test	yes	yes <sup>a</sup>
870.5395 Mutagenicity—Mammalian Erythrocyte Micronucleus Test	yes	yes
870.6100 28-Day Delayed Neurotoxicity in Hens.....	yes	yes
870.6200a Acute Neurotoxicity Screening Battery in Rats .....	yes	yes
870.6200b 90-Day Neurotoxicity Screening Battery in Rats .....	yes	yes <sup>b</sup>
870.6300 Developmental Neurotoxicity.....	yes	yes <sup>b</sup>
870.7800 Immunotoxicity	yes	yes <sup>c</sup>
Special Studies		
Comparative Cholinesterase in Rats .....	yes	yes

a Although there were no guideline 870.5385 studies submitted, there are mutagenicity studies which evaluate both somatic and germinal cells, which is considered sufficient to satisfy CFR requirements.

b Study not required by HASPOC (Leshin, 2015, TXR # 0057280).

c (van Alstine, 2013, TXR # 0056738)

## A.2 Summary of OPP's ChE Policy & Use of BMD Modeling

OPP's ChE policy (USEPA, 2000<sup>15</sup>) describes the manner in which ChE data are used in human health risk assessment. The following text provides a brief summary of that document to provide context to points of departure selected.

ChEI can be inhibited in the central or peripheral nervous tissue. Measurements of AChE or ChE inhibition in peripheral tissues (e.g., liver, diaphragm, heart, lung, etc.) are rare. Experimental laboratory studies generally measure brain (central) and blood (plasma and RBC) ChE. Blood measures do not represent the target tissue, but are instead used as surrogate measures for peripheral toxicity in studies with laboratory animals or for peripheral and/or central toxicity in humans. In addition, RBC measures represent AChE, whereas plasma measures are predominately butyryl-ChE (BuChE). RBC AChE data are expected to provide a better representation of the inhibition of AChE in target tissues. As part of the dose response assessment, evaluations of neurobehavior and clinical signs are performed to consider the dose response linkage between ChEI and apical outcomes.

Refinements to OPP's use of ChE data have come in the implementation of BMD approaches in dose response assessment. Beginning with the OP CRA, OPP has increased its use of BMD modeling to derive PODs for AChE inhibiting compounds. Most often, the decreasing exponential empirical model has been used.

OPP does not have a defined benchmark response (BMR) for OPs. However, the 10% level has been used in the majority of dose response analyses conducted to date. This 10% level represents a 10% reduction in AChE activity (i.e., inhibition) compared to background (i.e., controls). Specifically, the BMD<sub>10</sub> is the estimated dose where ChE is inhibited by 10% compared to background. The BMDL<sub>10</sub> is the lower confidence bound on the BMD<sub>10</sub>.

The use of the 10% BMR is derived from a combination of statistical and biological considerations. A power analysis was conducted by the Office of Research and Development (ORD) on over 100 brain AChE datasets across more than 25 OPs as part of the OP CRA (USEPA, 2002). This analysis demonstrated that 10% is a level that can be reliably measured in the majority of rat toxicity studies. In addition, the 10% level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity in the brain compartment and is a response level close to the background brain ChE level. With respect to biological considerations, a change in 10% brain ChEI is protective for downstream clinical signs and apical neurotoxic outcomes. With respect to RBC ChEI, these data tend to be more variable than brain AChE data. OPP begins its BMD analyses using the 10% BMR for RBC ChEI, but BMRs up to 20% could be considered on a case by case basis as long as such PODs are protective for brain ChEI, potential peripheral inhibition, and clinical signs of neurotoxicity.

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<sup>15</sup> USEPA (2000) Office of Pesticide Programs, US Environmental Protection Agency, Washington DC 20460. August 18, 2000 Office of Pesticide Programs Science Policy of The Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides.

The results of the BMD modeling for the bensulide are as follows:

<b>Table A.2.1. Results of BMD Modeling (mg/kg) for Brain and RBC ChE Data on Bensulide, Acute Oral Dosing Studies in Rats.</b>					
<b>Test</b>	<b>Age Sex</b>	<b>Brain BMD<sub>10</sub></b>	<b>Brain BMDL<sub>10</sub></b>	<b>RBC BMD<sub>10</sub></b>	<b>RBC BMDL<sub>10</sub></b>
MRID 49433502 Acute CCA	Adult Male	79.94	63.10	79.11	55.92
MRID 49433502 Acute CCA	Adult Female	46.39	36.88	27.21	21.53
MRID 49433502 Acute CCA	PND 11 Male	26.04	16.67	17.74	11.61
MRID 49433502 Acute CCA	PND 11 Female	28.90	21.30	16.23	11.24
MRID 43195901 Acute Neurotoxicity	Adult Male	149.72	95.46	QF	
MRID 43195901 Acute Neurotoxicity	Adult Female	QF		37.29	30.30

CCA = Comparative Cholinesterase Assay

QF = Questionable fit, all statistical tests of fit were not passed and/or high variance was observed in the dose groups

<b>Table A.2.2. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Bensulide, Repeated Oral Dosing Studies in Rats.</b>					
<b>Test (Dosing Days)</b>	<b>Age Sex</b>	<b>Brain BMD<sub>10</sub></b>	<b>Brain BMDL<sub>10</sub></b>	<b>RBC BMD<sub>10</sub></b>	<b>RBC BMDL<sub>10</sub></b>
MRID 44161101 Chronic/Carc, 103W	Adult Male	NE		NE	
MRID 44161101 Chronic/Carc, 103W	Adult Female	NE		11.68	7.83
MRID 44161101 Chronic/Carc, 77W	Adult Male	NE		NE	
MRID 44161101 Chronic/Carc, 77W	Adult Female	NE		6.63	4.53
MRID 44161101 Chronic/Carc, 51W	Adult Male	29.58	16.20	NF	
MRID 44161101 Chronic/Carc, 51W	Adult Female	26.26	14.97	4.19	3.77
MRID 44161101 Chronic/Carc, 25W	Adult Male	25.68	18.15	4.51	2.77
MRID 44161101 Chronic/Carc, 25W	Adult Female	NF		7.26	5.16
MRID 43919601 Subchronic rat, 13W	Adult Male	NE		NE	
MRID 43919601 Subchronic rat, 13W	Adult Female	NE		9.53	7.19
MRID 49454001 Gestational CCA, 13D	Dam	23.52	21.54	12.01	10.03
MRID 49454001 Gestational CCA, 13D	Fetus Male	27.08	21.92	22.34	17.19
MRID 49454001 Gestational CCA, 13D	Fetus Female	31.37	24.38	21.82	17.40
MRID 49466201 Repeated-Dose CCA, 10D	Adult Male	NT		NT	
MRID 49466201 Repeated-Dose CCA, 10D	Adult Female	31.04	25.87	18.66	15.92
MRID 49466201 Repeated-Dose CCA, 10D	PND 11 Male	19.60	15.67	7.91	5.92
MRID 49466201 Repeated-Dose CCA, 10D	PND 11 Female	17.30	12.87	12.30	9.05
MRID 43948701 2 gen repro	F0 Male	QF		197.77	132.68
MRID 43948701 2 gen repro	F0 Female	312.99	83.08	114.32	91.53
MRID 43948701 2 gen repro	F1 Male	QF		QF	
MRID 43948701 2 gen repro	F1 Female	466.83	214.75	QF	

CCA = comparative cholinesterase assay

NF = No model fit the data well

NE = Not evaluated

NT = Not tested

NDR = No dose response found upon analysis

NA = Result considered not accurate

QF = Questionable fit, all statistical tests of fit were not passed and/or high variance was observed in the dose groups

Tox = Toxicity

Carc = Carcinogenicity

**Chronic dog:** no apparent dose response for male and female brain ChEI, and no fit due to too much variance for male and female RBC ChEI.

**Dermal toxicity:** no apparent dose response (did not model) for both sexes and both brain and RBC ChEI. The LOAEL was not established in MRID 42162002 (NOAEL = 1000 mg/kg/day). The LOAEL was 500 mg/kg/day in MRIDs 44801101 and 44809401 based on decreased plasma and brain ChE (no RBC ChEI), and the NOAEL = 50 mg/kg/day.

### Bensulide Toxicity Profiles follow:

<b>Table A.2.3. Acute Toxicity Profile – Bensulide</b>				
<b>Guideline No.</b>	<b>Study Type</b>	<b>MRID #</b>	<b>Results</b>	<b>Toxicity Category</b>
870.1100	Acute oral [rat]	00097921 92005011	LD <sub>50</sub> = 360 mg/kg (M) LD <sub>50</sub> = 270 mg/kg (F)	II
870.1200	Acute dermal [rat]	41597501	LD <sub>50</sub> ≥ 2000 mg/kg	III
870.1200	Acute dermal [rabbit]	00097921	LD <sub>50</sub> > 5000 mg/kg	IV
870.1300	Acute inhalation [rat]	41646201	LC <sub>50</sub> > 1.75 mg/L	III
870.2400	Acute eye irritation [rabbit]	41597502	mild irritant	III
870.2500	Acute dermal irritation [rabbit]	00097921 92005012	mild irritant	IV
870.2600	Dermal sensitization [guinea pig]	00160075	not a sensitizer	NA

<b>Table A.2.4. Subchronic, Chronic, and Other Toxicity Profile – Bensulide</b>		
<b>Guideline No./Study Type</b>	<b>MRID No. (year)/ TXR #/ Classification /Doses</b>	<b>Results</b>
870.3100a 90-Day oral toxicity rodents - rat	43919601 (1992) TXR 0012289 Acceptable, guideline 0, 5, 15, 45, or 100 mg/kg/day	NOAEL = 5 mg/kg/day LOAEL = 15 mg/kg/day based on decreased plasma ChE in both sexes and brain ChE in males  At 45 and 100 mg/kg/day, decreased RBC and brain ChE in both sexes and liver vacuolation in males. At 100 mg/kg/day, increased ALT in both sexes, fatty microvesicles in males, and liver weight in males
870.3100b 90-Day oral toxicity rodents - mouse	44161104 (1993) TXR 0012289 Acceptable, guideline 0, 30, 100, 300, or 1000 mg/kg/day	NOAEL = 300 mg/kg/day LOAEL = 1000 mg/kg/day based on decreased body weight in males, increased liver weight, liver lobulation hepatocyte hypertrophy in both sexes, liver enlargement in males, decreased ovarian and spleen weights in females

**Table A.2.4. Subchronic, Chronic, and Other Toxicity Profile – Bensulide**

<b>Guideline No./Study Type</b>	<b>MRID No. (year)/ TXR #/ Classification /Doses</b>	<b>Results</b>
870.3150b 90-Day oral toxicity non-rodents - dogs	44052703 (2016) TXR 0057338 Acceptable, guideline 0, 1, 3, 10, or 30 mg/kg/day	NOAEL = 10 mg/kg/day LOAEL = 30 mg/kg/day based conservatively on increased liver weight, increased incidence of liver lipid deposits, and increased activated partial thromboplastin times
870.3200 21-Day dermal toxicity with parent - rat	42162002 (1991) TXR 0009325 Acceptable, guideline 0, 10, 100, or 1000 mg/kg/day	NOAEL $\geq$ 1000 mg/kg/day LOAEL was not established
870.3200 21-Day dermal toxicity with parent - rat	44801101 and 44809401 (1999) TXR 0013532 Acceptable, non- guideline 0, 30, 50, or 500 mg/kg/day (6 h/d, 21 d)	NOAEL = 50 mg/kg/day LOAEL = 500 mg/kg/day based on decreased plasma and brain ChE  Note: No effect was noted on RBC ChE in either sex at any time point.
870.3700a Prenatal developmental - rat	00146585 (1985) 92005018 (1990) TXR 0012289 Acceptable, guideline 0, 5.5, 23.0, or 95.0 mg/kg/day	Maternal NOAEL = 5.5 mg/kg/day Maternal LOAEL = 23.0 mg/kg/day based on decreased plasma ChE In the 95.0 mg/kg/day dams, tremor and decreased BWG, FC, whole and corrected (uterine wt) BW were noted.  Developmental NOAEL $\geq$ 95.0 mg/kg/day Developmental LOAEL was not established
870.3700b Prenatal developmental - rabbit	00152845 (1985) 92005019 (1990) TXR 0012289 Acceptable, guideline 0, 5, 20, or 80 mg/kg/day	Maternal NOAEL = 20 mg/kg/day Maternal LOAEL = 80 mg/kg/day based on decreased body weights and weight loss during the treatment interval  Developmental NOAEL $\geq$ 80 mg/kg/day Developmental LOAEL was not established

**Table A.2.4. Subchronic, Chronic, and Other Toxicity Profile – Bensulide**

<b>Guideline No./Study Type</b>	<b>MRID No. (year)/ TXR #/ Classification /Doses</b>	<b>Results</b>
870.3800 Reproduction and fertility effects with parent - rat	43948701 (1996) TXR 0012289 Acceptable, guideline Pre-mating doses: P male: 0, 2.0, 12.3, or 68.2 mg/kg/day P female: 0, 2.3, 13.2, or 80.8 mg/kg/day F1 male: 2.3, 14.0, or 86.5 mg/kg/day F1 female: 2.6, 15.4, or 93.2 mg/kg/day	Parental/Systemic NOAEL $\geq$ 68.2 mg/kg/day Parental/Systemic LOAEL was not established  ChE inhibition NOAEL was not established ChE inhibition LOAEL = 2.3 mg/kg/day based on plasma ChE inhibition in the F1 males  In the mid and high dose P males and females, plasma ChE was decreased. In the high dose P males and females, RBC ChE was decreased, and brain ChE was also decreased in females. At the mid and high dose, decreased RBC ChE was noted in F1 males, and plasma ChE was decreased in F1 females. In the high dose F1 females, RBC and brain ChE were decreased. In the high dose P males and females, low fertility rates were noted.  Reproductive NOAEL $\geq$ 68.2 mg/kg/day Reproductive LOAEL was not established  Offspring NOAEL = 15.4 mg/kg/day Offspring LOAEL = 93.2 mg/kg/day based on reduced F2 pup survival ChE not measured in pups.
870.4100b Chronic toxicity (1 year) - dogs	44066401 (2016) TXR 0057338 Acceptable, guideline M & F: 0, 0.5, 4, or 30 mg/kg/day	NOAEL = 4 mg/kg/day LOAEL = 30 mg/kg/day based on the RBC cholinesterase inhibition and mild indications of hepatotoxicity (Kupffer-cell accumulation, inflammation, and fatty
870.4100b Chronic toxicity (1 year) - dogs	41112301 (1989) 92005016 (1990) TXR 0008369 Acceptable, guideline M & F: 0, 2, 10, or 50 mg/kg/day	NOAEL = 10 mg/kg/day LOAEL = 50 mg/kg/day based on increased mortality, clinical signs of toxicity, decreased body weight and food consumption, discolored liver, and several microscopic lesions (fibrosis and chronic inflammation of the thymus, erythroid/myeloid bone marrow depletion, inflammation and/or degeneration of the skeletal muscle, and liver changes)
870.4200b Carcinogenicity with parent - mice	44161105 (1996) TXR 0012289 Acceptable, guideline M & F: 0, 1, 50, or 200 mg/kg/day	NOAEL = 1 mg/kg/day LOAEL = 50 mg/kg/day based on decreased plasma and erythrocyte ChE in both sexes, brain ChE in females, and body weight gain in males  At 200 mg/kg/day, increased liver weight and liver pathology (clear cell foci, hepatocyte pigmentation, Kupffer cell pigmentation, and atypia) <b>Carcinogenic potential is considered negative.</b>

**Table A.2.4. Subchronic, Chronic, and Other Toxicity Profile – Bensulide**

Guideline No./Study Type	MRID No. (year)/ TXR #/ Classification /Doses	Results
870.4300 Combined chronic toxicity/Carcinogenicity - rats	43919602 (1995) 44161101 (1996) TXR 0012289 Acceptable, guideline M & F: 0, 1, 15, or 60 mg/kg/day	NOAEL = 1 mg/kg/day LOAEL = 15 mg/kg/day based on decreased plasma and erythrocytes ChE in both sexes <b>Carcinogenic potential is considered negative.</b>
870.5100 Bacterial reverse mutation test with parent	00153493 (1984) 00153495 (1984) 92005021 (1990) TXR 0012289 Acceptable, guideline 0, 0.005, 0.014, 0.041, 0.123, 0.370, 1.111, 3.333, 10, 25, or 50 μL/plate (TA100); 0, 0.037, 0.111, 0.333, 1, or 3 μL/plate (TA98, TA1535, and TA1537)	There was no evidence of induced mutant colonies over background in <i>Salmonella typhimurium</i> strains TA98, TA100, TA1535, and TA1537.
870.5300 Mouse lymphoma cell/mammalian activation gene forward mutation assay (TK locus) with parent.	43273901 (1994) TXR 0011409 Acceptable, guideline 0, 8, 14, 16, 21, 24, 28, 32, 35, 40, or 42 μg/mL (-S9); 0, 16, 24, 28, 32, 35, 40, 42, 48, 49, or 56 μg/plate (+S9)	There was no evidence of induced forward mutation at the TK locus.
870.5375 <i>In vitro</i> mammalian cytogenetics (Chromosomal aberration assay in human peripheral blood)	41902601 (1990) TXR 0009077 Unacceptable, guideline (upgradable) 0, 5, 40, 60 or 80	Bensulide was not clastogenic under conditions of the assay.  Study deficiencies included: lack of information concerning: stability of test compound; criteria for assessing chromosomal aberrations; level of p value used in determining statistical significance; and potential for bensulide-induced delay of cell cycle.
870.5395 <i>In vivo</i> mouse micronucleus	41902602 (1990) TXR 0010229; 0009077 Acceptable, guideline M & F: 0, 250, or 400 mg/kg/day	There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow.
870.6100 Delayed neurotoxicity (Acute) - hen	43334302 (1994) 43306301 (1994) TXR 0012289 Acceptable, guideline M: 0 or 2262 mg/kg	Bensulide did not induce acute delayed neurotoxicity in the hen at the limit dose.

**Table A.2.4. Subchronic, Chronic, and Other Toxicity Profile – Bensulide**

<b>Guideline No./Study Type</b>	<b>MRID No. (year)/ TXR #/ Classification /Doses</b>	<b>Results</b>
870.6200a Acute neurotoxicity - rat	43195901 (1994) TXR 0012289 Acceptable, guideline M: 0, 30, 100, or 300 mg/kg F: 0, 15, 50, or 150	NOAEL = 100 mg/kg/day LOAEL = 150 mg/kg/day based on decreased plasma, RBC, and brain ChE in females and minimal, clinical signs consistent with ChE inhibition in females
870.6200b Subchronic neurotoxicity screening battery - rat	NA	NA
870.6300 Developmental neurotoxicity study with parent	NA	NA
870.7485 Metabolism and pharmacokinetics with parent - rat	42007901 (1991) 42007902 (1991) 42007903 (1991) 42007904 (1991) 42225401 (1992) TXR 0009491; 0012289; 0012948 Acceptable, guideline single 1 mg/kg dose, 1 mg/kg/day for 15 consecutive days, single 100 mg/kg dose, 50 mg/kg for 4 consecutive days	In a rat metabolism study with <sup>14</sup> C-labeled bensulide, Sprague-Dawley rats received doses of 1 mg/kg (single, low dose), 1 mg/kg × 15 days (repeated low dose), 50 mg/kg/day × 4 consecutive days (group used for metabolite isolation), and 100 mg/kg (single, high dose). Bensulide was excreted primarily in the urine, with the majority of the dose eliminated within 24 hours. Fecal excretion also occurred; biliary excretion was minimal. The highest concentration of radioactivity was found in whole blood, associated with the cellular component. Whole body auto radiography showed a much higher level of radioactivity remaining in males after 24 hours than in females. Four metabolites were identified. One was the primary urinary metabolite and the other identified metabolites were found in the urine. The proposed formation of two metabolites involved the cleavage of the PO <sub>2</sub> [CH(CH <sub>3</sub> ) <sub>2</sub> ] <sub>2</sub> moiety of bensulide, followed by methylation and oxidation of the sulphur atom. Conjugation with glycine or carboxylation and oxidative desulphuration is proposed to lead to the other two identified metabolites.
870.7600 Dermal penetration-rat	NA	NA
870.7800 Immunotoxicity - mice	48377701 (2011) 48623701 (2011) TXR 0055808; 0056257 Unacceptable, guideline 0, 50, 200, or 800 mg/kg/day	Increased mortality was observed at 800 mg/kg/day. Problems with the conduct of the TDAR made confident interpretation of the results impossible.  HASPOC waived this study (van Alstine, 2013, TXR # 0056738)

**Table A.2.4. Subchronic, Chronic, and Other Toxicity Profile – Bensulide**

Guideline No./Study Type	MRID No. (year)/ TXR #/ Classification /Doses	Results
Non-Guideline Comparative cholinesterase assay – rat	<p>49433502 (2014) 49466201 (2014) 49454001 (2014) Acceptable, non-guideline</p> <p>Animals were treated with a single gavage dose in corn oil at 0, 50, 100, 150, and 200 mg/kg/day in the adult males, 0, 25, 50, 100, and 150 mg/kg/day in adult females, and 0, 20, 40, 60, and 100 mg/kg/day in the pups</p> <p>Animals were treated once daily for 10 consecutive days at 0, 15, 25, 50, and 75 mg/kg/day in the adults and 0, 5, 10, 20, 40, and 60 mg/kg/day in the pups.</p> <p>Dams were treated once daily during GD 6-20 (inclusive) at 0, 15, 30, 60, and 90 mg/kg/day</p>	<p>In the acute study, the LOAEL in adults was 50 mg/kg/day based on ChE inhibition in the RBC and brain of females. The NOAEL was 25 mg/kg/day. The LOAEL in the PND 11 pups was 40 mg/kg/day based on ChE inhibition in the RBC and brain of males and females. The NOAEL was 20 mg/kg/day.</p> <p>In the repeated dose study, the LOAEL in adults was 25 mg/kg/day based on ChE inhibition in the RBC of females (only sex tested). The NOAEL was 15 mg/kg/day. The LOAEL in the PND 11 pups was 10 mg/kg/day based on ChE inhibition in the RBC of males. The NOAEL was 5 mg/kg/day.</p> <p>In the gestational study, the LOAEL in dams and fetuses was 30 mg/kg/day based on ChE inhibition in RBC and brain. The NOAEL was 15 mg/kg/day.</p>

### A.3 Executive Summaries

#### A.3.1 Subchronic Toxicity

##### 870.3100 90-Day Oral Toxicity - Rat

In a subchronic toxicity study (**MRID 43919601**), male and female Sprague-Dawley rats (10/sex/dose) were given bensulide (92.4% a.i.) in the diet for 13 weeks at doses of 0, 5, 15, 45, or 100 mg/kg/day.

Significantly decreased body weight gains ( $p < 0.01$ , 19%) were observed for male rats at 100 mg/kg/day. Although not significant, body weight gains for female rats were 12,

11, and 14% lower than controls at 15, 45, and 100 mg/kg/day, respectively. Food consumption appeared not affected by treatment. Overall food efficiency was decreased in males at 100 mg/kg/day.

Significantly increased alanine amino-transferase levels were observed at 45 mg/kg/day (87% increase in males; 48%, females) and 100 mg/kg/day (145%, males and 90%, females). Dose-related inhibition of ChE activity occurred in both sexes. Relative to controls, plasma ChE decreases were 28, 54, and 62% (males) at 15, 45, and 100 mg/kg/day, respectively, and 19, 47, 84, and 90% (females) at 5, 15, 45, and 100 mg/kg/day, respectively. Red blood cell ChE decreases were 47 and 59% (males) and 38 and 66% (females) at 45 and 100 mg/kg, respectively. Brain ChE decreases were 18 and 43% (males) at 15 and 100 mg/kg/day, respectively, and 28 and 58% (females) at 45 and 100 mg/kg, respectively. Increased relative liver weights were observed in males (17%,  $p<0.01$ ) and females (19%,  $p<0.001$ ) at 100 mg/kg/day. The hepatic toxicity was corroborated by mild histological changes in the liver in males (fatty microvesicles at 100 mg/kg/day; vacuolation at 45 and 100 mg/kg/day).

Under the conditions of this study, the NOAEL is 5 mg/kg/day; the LOAEL is 15 mg/kg/day, based on decreased plasma ChE activity in both sexes, decreased brain ChE activity in males, and an equivocal reduction in body weight gain in females.

This subchronic dietary toxicity study in rats is classified as Acceptable/Guideline and satisfies the guideline requirements (§82-1a) for a subchronic toxicity study in the rat.

### **870.3100 90-Day Oral Toxicity - Mouse**

Reviewed as the dose-selection rational for the chronic toxicity study (MRID 44161105).

The rational for dose selection was based on results from 0 previously conducted 13-week subchronic study in which 10 CD-1 mice/sex/dose were dosed with bensulide ( $92.4 \pm 0.5\%$ ; Lot # CBI 0801) at 0, 30, 100, 300, or 1000 mg/kg/day (MRID 44161104). All animals, including premature decedents were necropsied. After necropsy, the kidneys and lungs of the controls and high-dose animals and the livers of all the animals were examined histologically. The brain, heart, kidneys, liver, lungs, ovaries, spleen, and testes were weighed. Mortality, clinical signs, and water consumption were not affected by treatment with bensulide. There were no treatment related findings in the 30 mg/kg/day animals. The following treatment related findings were observed in the 1000 mg/kg/day animals compared to concurrent controls: decreased mean body weight gain in females ( $\downarrow 50\%$ ;  $p<0.01$ ) and decreased body weight in males ( $\downarrow 1$  g;  $p<0.001$ ); decreased overall (weeks 1-13) feed consumption in both sexes ( $\downarrow 9-10\%$ ); increased liver weight ( $\uparrow 72-90\%$ ;  $p<0.001$ ) and increase in liver lobulation in both sexes; liver enlargement in males; increase in the incidence and severity of hepatocyte hypertrophy in both sexes; and a decrease in ovarian ( $\downarrow 43\%$ ;  $p<0.001$ ) and spleen ( $\downarrow 26\%$ ;  $p<0.05$ ) weights in females. Findings in the 100 and 300 mg/kg/day dose groups consisted of a reduction in body weight gain in the males ( $\downarrow 27$  and  $55\%$ ;  $p<0.001$ , respectively), an increase in liver

weights in both sexes ( $\uparrow$ 19-42%;  $p < 0.01$  and  $< 0.001$ ), and an increase in the incidence and/or the severity of hepatocyte hypertrophy in the animals of both groups.

#### **870.3150 90-Day Oral Toxicity – Dog**

In a 13-week subchronic toxicity study (MRID 44052703), bensulide (92.4% a.i., Lot #CBI 0801) was administered via the diet to four dogs/sex/group at dose levels of 0, 1, 3, 10, or 30 mg/kg/day for 13 weeks.

No treatment-related effects were noted on survival, clinical signs, body weights, food consumption, ophthalmology findings, clinical chemistry (including RBC and brain cholinesterase but excluding plasma cholinesterase), urinalysis, and necropsy.

At 30 mg/kg/day, there was slight evidence for liver toxicity. Adjusted (for terminal body weight covariate) liver weight means were decreased by 19-22% in both sexes. There was no statistical difference in liver weights at this dose in the chronic toxicity study in dogs. Additionally, periportal lipid deposits were noted in the liver of 7/8 rats, and the eighth rat (a female) had centrilobular lipid deposits. The severity was reported as only very mild or mild. The increase in weight was considered slight, and the biological significance of the lipid deposits was unclear, but likely negligible considering the severity. However, liver findings following bensulide treatment have been reported in rats and mice, as well as in the chronic toxicity study in dogs. Activated partial thromboplastin times were prolonged in both sexes in the 30 mg/kg/day treatment group at 6 (21-35%) and 13 (33-50%) weeks; this parameter was not evaluated in the chronic toxicity study in dogs. The liver effects and hematological effect were together considered very conservatively to be adverse.

**The LOAEL was 30 mg/kg/day, based conservatively on increased liver weight, increased incidence of liver lipid deposits, and increased activated partial thromboplastin times. The NOAEL is 10 mg/kg/day.**

This study is classified **acceptable, guideline** and satisfies the guideline requirements (OCSPP 870.3150; OECD 409) for a 90-day oral toxicity study in dogs.

#### **870.3200 21/28-Day Dermal Toxicity – Rat**

In a 21-day dermal toxicity study (MRID 42162002), male and female specific pathogen-free Wistar-derived albino rats (Alpk:APfSD strain; 5/sex/dose; 6-8 weeks old) were dermally treated over a 5 cm x 10 cm area of clipped dorso-lumbar skin with bensulide technical (92.7% a.i.) at dose levels of 0 (sham control), 10, 100, and 1000 mg/kg/day (limit test dose). Dosing occurred 21 times over a period of 30 days (five days/week). Following each dosing, the application site was covered with an occlusive dressing (gauze patch, a patch of plastic film secured by adhesive bandages, and two pieces of 2.5 cm-wide PVC tape wrapped around the animals) for approximately 6 hours.

After each 6-hour exposure period, the dressings were removed and the application sites washed with warm water. On dosing days, animals were fitted with Elizabethan collars to prevent test substance ingestion. Rats were observed for clinical signs and dermal irritation prior to dosing, after each removal of dressings, and at least once daily during non-dosing days. They were weighed daily, and food consumption was recorded twice weekly. At study termination, cardiac blood samples were collected shortly after animal sacrifice for hematological and clinical chemistry determinations. Gross necropsies were conducted, the standard set of organs were fixed for potential histopathology, and the following organs were also weighed: adrenals, brain, kidneys, liver, and testes (males). Only the kidneys of all animals, and the treated and untreated skins and livers of the control (0 mg/kg/day) and high-dose (1000 mg/kg/day) were examined histologically.

There were no deaths, compound-related clinical signs, or significant changes in body weight or food consumption in any group. A small incidence of dermal trauma was apparently caused by the bandages. No abnormal hematology was seen, and the only clinical chemistry anomaly was a 43% decrease in plasma triglycerides in the high-dose (1000 mg/kg/day) males compared to controls; females were not affected. In the absence of other findings, this decrease is of unknown biological significance. There were no dose-related gross lesions or organ weight changes. Some scabbing of treated and untreated skin, due to bandage trauma, was observed in all groups. This observation correlates with several histopathologic findings of slight to minimal acanthosis, parakeratosis, and inflammatory infiltration in treated and untreated skin. A number of minimal to slight renal lesions were observed, but they are not clinically significant and may have represented artifacts. Therefore, the NOAEL is > 1000 mg/kg/day (limit dose), based on the lack of any observed toxicity, and the LOAEL was not determined.

Although **cholinesterase activity was not determined**, this study was classified as Acceptable/Guideline and satisfies the Guideline requirement for a 21-day dermal toxicity study (82-2) in the rat.

In a special 21-day dermal toxicity study (**MRIDs 44801101 and 44809401**), groups of Charles River CD rats (10/sex/dose) were dermally applied Bensulide technical (92.1%) at dose levels of 0, 30, 50, and 500 mg/kg for 6 hrs/day for 21 days. The test chemical did not produce treatment-related clinical signs, mortality, or changes in body weight and food consumption. Clinical chemistry and hematology parameters were not measured. Urinalysis, and organ weights were not determined. However, these parameters were not significantly affected in a previous 21-day dermal toxicity study in rats which were dermally treated up to 1000 mg/kg (MRID 42162002; Tox. Doc. No. 009325).

Bensulide at 500 mg/kg produced statistically significant decreases ( $p < 0.01$ ) in plasma cholinesterase (PChE) activity in both males and females on days 7, 14, and 22; the decrease (-31% in males & -55% in females) was particularly marked at the end of the study (day 22). In addition, the inhibition of PChE appeared to increase with the

increased time of treatment. Plasma cholinesterase inhibition was also seen in 50 mg/kg females, but it was not statistically significant. Bensulide at 500 mg/kg also significantly ( $p < 0.05$ ) inhibited brain stem ChE activity in both males and females, but it had no effect on the ChE activity in cerebellum and cerebral cortex. In this study, RBC ChE activity was not affected by bensulide.

Therefore, under the conditions of this dermal toxicity study, the LOAEL for ChE inhibition was 500 mg/kg based on significant inhibition of both brain and PChE activity, and the NOAEL was 50 mg/kg.

The study was classified as Acceptable/non-guideline because this was a special study conducted to obtain information on the potential of bensulide to inhibit ChE activity in plasma, RBC, and brain.

#### **870.3465 90-Day Inhalation – Rat (Not Submitted but Required)**

### **A.3.2 Prenatal Developmental Toxicity**

#### **870.3700a Prenatal Developmental Toxicity Study – Rat**

In a developmental toxicity study (**MRID 00146585**), bensulide technical (92.8 % a.i.) was administered to 25 or 26 female Sprague-Dawley rats/dose in corn oil by gavage at analytically determined dose levels of 0, 5.5, 23.0 or 95.0 mg/kg/day from days 6 through 20 of gestation.

Bensulide technical exerted no effects on maternal gross pathology, fertility, or cesarian parameters. The maternal systemic LOAEL is 95.0 mg/kg/day (HDT), based on tremors, decreased body weight (range: 93-94% of control value) on days 12, 16, and 21 of gestation, decreased body weight gain during days 9-12 (25% control value) and 6-21 (76% of control value) of gestation, decreased (79% of control value) feed intake during days 13-16 of gestation, and decreased whole and corrected (reproductive tract subtracted) body weights (93% and 91% of control values, respectively) and increased liver/body weight ratio (112% of control value) at study termination. The maternal systemic NOAEL is 23.0 mg/kg/day (MDT).

The Maternal NOAEL for cholinesterase inhibition is 5.5 mg/kg/day (LDT), based on a 48% decrease in plasma ChE activity at 23.0 mg/kg/day (LOAEL; MDT) in the absence of any other effects.

The Developmental NOAEL > 95.0 mg/kg/day (HDT), based on the lack of any developmental effects. The developmental LOAEL > 95.0 mg/kg/day.

This developmental toxicity study in the rat is classified Acceptable/Guideline and does satisfy the guideline requirement for a developmental toxicity study (§83-3a) in the rat.

**870.3700b Prenatal Developmental Toxicity Study - Rabbit**

In a developmental toxicity study (MRID 00152845), inseminated New Zealand White rabbits, randomly assigned to one control and three treatment groups of 18 animals each, were administered Betasan® (bensulide technical; 92.8% a.i.) by oral gavage at doses of 0, 5, 20, or 80 mg/kg/day on gestation days (GD) 7-19, inclusive. Cesarean section examinations were performed on all surviving does on GD 29, followed by teratological examination of all fetuses.

No treatment-related effects were observed in the 5 or 20 mg/kg/day groups as compared with controls. Three high-dose animals aborted, one each on GD 18, 27, and 28, and were sacrificed and necropsied. All other animals survived until scheduled sacrifice. Decreased defecation was observed in 3, 2, 1, and 11 animals and decreased urination was observed in 3, 2, 0, and 11 animals in the control, 5, 20, and 80 mg/kg/day groups, respectively. No other dose- or treatment-related clinical signs of toxicity were observed during the study. Maternal body weight gains were significantly ( $p \leq 0.05$  or  $0.01$ ) less in the high-dose group as compared to the controls throughout the dosing interval with an overall weight loss recorded during the treatment interval. Absolute body weights of the high-dose animals were less than the controls beginning on GD 13 but statistical significance ( $p \leq 0.01$ ) was reached only on GD 19. After cessation of treatment, does in the high-dose group showed recovery with body weight gains significantly ( $p \leq 0.01$ ) greater than the controls. During the dosing interval, food consumption by the high-dose animals was significantly ( $p \leq 0.01$ ) less than the control beginning on GD 10. Overall food consumption was significantly less in the high-dose group for the entire dosing interval (62%;  $p \leq 0.01$ ) and the entire gestation period (83%;  $p \leq 0.05$ ) as compared to controls.

Therefore, the maternal toxicity NOAEL is 20 mg/kg/day and the maternal toxicity LOAEL is 80 mg/kg/day based on reduced body weights and weight loss during the treatment interval.

There were no differences between treated and control groups for live fetuses/litter, fetal body weights, or fetal sex ratios. No treatment-related malformations/variations were observed for any external, visceral, or skeletal parameter examined of kits in the treated litters as compared to the control litters. There was no difference in the total number of litters containing fetuses with major malformations as compared to controls: 3/15, 1/15, 0/10, and 2/10 affected in the control, 5, 20, and 80 mg/kg/day groups, respectively.

Therefore, the developmental toxicity NOAEL is  $> 80$  mg/kg/day and the developmental toxicity LOAEL was not identified.

This developmental toxicity study in rabbits is classified as Acceptable/Guideline and satisfies the guideline requirement (§83-3b) for a developmental toxicity study in rabbits.

### A.3.3 Reproductive Toxicity

#### 870.3800 Reproduction and Fertility Effects – Rat

In a two-generation reproduction study (MRID 43948701), Bensulide (92.4% a.i.; Lot No. CDI 0801) was administered to male and female Sprague-Dawley CD rats in the diet at concentrations of 0, 25, 150, or 900 ppm for two generations. Premating doses for the F<sub>0</sub> males were 2.0, 12.3, and 68.2 mg/kg, respectively, and for the F<sub>0</sub> females were 2.3, 13.2, and 80.8 mg/kg, respectively. Premating doses for the F<sub>1</sub> males were 2.3, 14.0, and 86.5 mg/kg, respectively, and for the F<sub>1</sub> females were 2.6, 15.4, and 93.2 mg/kg, respectively. The F<sub>0</sub> generation contained 28 animals/sex/dose and the F<sub>1</sub> generation contained 24 animals/sex/dose. Animals were given test or control diet for at least 10 weeks then mated within the same dose group.

F<sub>1</sub> animals were weaned on the same diet as their parents. At least 21 litters were produced in each generation. All animals were exposed to test material either in the diet or during lactation until sacrifice.

Although several deaths occurred among treated and control groups of both generations, these were considered incidental to treatment. No overt treatment-related clinical signs of toxicity were observed in the adult animals of either sex or generation. There were no statistically significant differences between treated and control groups of either sex or generation for absolute body weights, body weight gains, food consumption, or gross or histopathological findings.

Therefore, the NOAEL for systemic effects > 900 ppm (82.8 mg/kg/day; HDT) and the LOAEL was not determined.

Terminal cholinesterase activity was measured in plasma, red blood cell, and brains of the adult animals of both generations. Baseline or pretreatment activities were not measured. In F<sub>0</sub> males, plasma cholinesterase activity was significantly ( $p \leq 0.01$ ) reduced in the mid- and high- dose groups as compared to controls with percent inhibition (%I) 21 and 54%, respectively. High-dose F<sub>0</sub> males also had significantly ( $p \leq 0.01$ ) reduced RBC activity (%I = 32). Mid- and high-dose F<sub>0</sub> females had significantly ( $p \leq 0.01$ ) reduced plasma activity (%I = 43 and 76, respectively) while high-dose F<sub>0</sub> females also had significantly ( $p \leq 0.01$ ) reduced RBC (%I = 57) and brain (%I = 68) activities. Plasma activity was significantly ( $p \leq 0.01$ ) reduced in all treated F<sub>1</sub> male groups as compared to controls (%I = 28, 30, and 62, respectively). Mid- ( $p \leq 0.05$ ) and high-dose ( $p \leq 0.01$ ) F<sub>1</sub> males also had significantly reduced RBC activity (%I = 11 and 42, respectively). Mid- and high-dose F<sub>1</sub> females had significantly ( $p \leq 0.01$ ) reduced plasma activity (%I = 47 and 80, respectively) while high-dose F<sub>1</sub> females also had significantly ( $p \leq 0.01$ ) reduced RBC and brain activities (%I = 63 and 51). The 51-68% inhibition of brain ChE activity in females in the high-dose (900 ppm) group indicates that dosing was conducted at an adequately high level; higher doses would likely yield an unacceptable level of mortality.

Therefore, the LOAEL for cholinesterase inhibition is 25 ppm (2.3 mg/kg/day; LDT) based on inhibition of plasma enzyme activity in F<sub>1</sub> males. The cholinesterase inhibition NOAEL was not identified.

No statistically significant differences occurred for absolute body weights, body weight gains, or food consumption of the F<sub>0</sub> or F<sub>1</sub> females during gestation or lactation for any treated group as compared to controls. High-dose F<sub>0</sub> males and females had low fertility indices with only 21 of 28 males siring litters and only 24 of 28 females becoming pregnant. However, this effect was not repeated in the F<sub>1</sub> generation. There were no statistically significant differences between treated and control groups for number of litters or pups/litter during lactation of either generation.

Survival and viability of the F<sub>1</sub> pups was similar between treated and control groups. However, survival was greatly reduced in the high-dose F<sub>2</sub> pups with overall (day 0-21) survival only 61%. This was due mainly to a low viability index of 74% for lactation days 0-4.

Therefore, the LOAEL for reproductive toxicity is 900 ppm (93.2 mg/kg/day; HDT) based on reduced F<sub>2</sub> pup survival. The corresponding NOAEL for reproductive toxicity is 150 ppm (15.4 mg/kg/day; MDT).

This study is classified as Acceptable/Guideline and does satisfy the guideline requirement for a reproduction study (§83-4) in rats.

#### **A.3.4 Chronic Toxicity**

##### **870.4100a (870.4300) Chronic Toxicity – Rat**

##### **870.4100b Chronic Toxicity – Dog**

In a chronic toxicity study (MRID 44066401), bensulide (92.4% a.i.) was administered to four dogs/sex/dose by feeding at dose levels of 0, 0.5, 4, or 30 mg/kg/day for 52 weeks.

No treatment-related effects were noted on survival, clinical signs, body weights, food consumption, ophthalmology findings, urinalysis, and necropsy.

In the 30 mg/kg/day treatment group, there was inhibition ( $p \leq 0.05$ ) of RBC cholinesterase in females at Weeks 26 and 39 (↓32-39%) and in males at Week 52 (↓45%); however, decreases (not statistically significant) were noted in both sexes at all time points at this dose. No effect was clearly present on brain (pons and cerebellum) cholinesterase.

At 30 mg/kg/day, mild effects were also noted in the liver (primarily the female). An increased incidence of moderate focal pigmented Kupffer-cell accumulation (positive, for the presence of hemosiderin [Prussian Blue stain], neutral fat and diastase resistance [Periodic Acid Schiff stain]) was noted in 2/4 females compared to 0/4 controls (not

observed in any male). Focal liver inflammation occurred at a similar incidence in the treated dogs compared to controls (n=4, 3 treated males vs 3 controls; 4 treated females vs 3 controls); however, severity was increased (2 mild treated males vs 0 controls; 3 mild to moderate treated females vs 0 controls). The stain for fat was positive with a slightly increased incidence and severity in females (2/4 very mild to mild treated vs 1 very mild control). Liver weights were increased, but were not statistically different than the controls. Additionally, adjusted (terminal body weight covariate) adrenal gland weights were increased by 30% in males; however, there was no corroborating evidence of an adverse effect on the adrenals.

**The LOAEL for this study is 30 mg/kg/day based on the RBC cholinesterase inhibition and mild indications of hepatotoxicity (Kupffer-cell accumulation, inflammation, and fatty). The NOAEL is 4 mg/kg/day.**

This study is classified **acceptable, guideline** and satisfies the guideline requirement (OCSPP 870.4100b; OECD 452) for a chronic toxicity study in dogs.

#### **870.4100b Chronic Toxicity – Dog**

In a chronic toxicity study (MRID 41112301), bensulide (93.8% a.i.) was administered in the diet to five dogs/sex/dose at dose levels of 0, 2, 10, or 50 mg/kg/day for 52 weeks.

No treatment-related effects were noted on ophthalmology findings, urinalysis, and organ weights. No adverse effects were noted at 2 or 10 mg/kg/day.

At 50 mg/kg/day, excessive mortality was noted. In this group 9/10 dogs died or were terminated moribund. Mortality or morbidity typically was preceded by a drastic decrease in food consumption for 1-4 weeks prior to death. Clinical signs included those indicative of cholinesterase inhibition, as well as general malaise: loss of appetite, drastic weight loss, excessive salivation, tarry stools, red (bloody) stools, diarrhea, hypothermia, pale gum and mucous membranes, lethargy, and emaciation. Several dogs exhibited diarrhea, emesis, and/or excessive salivation beginning during the first week of the study. The single surviving female in this group exhibited occasional diarrhea, tarry stools, emesis, and excessive salivation. Body weight decreases in the males was progressive beginning after 3-11 weeks of treatment with mortality occurring after 8-21 weeks. Body weight decreases in the females that died or were terminated early was progressive beginning after 7-17 weeks of treatment with mortality occurring after 13-20 weeks. Anemia (as evidenced by decreased erythrocytes, hematocrit, and hemoglobin) was noted in the males and one female. Serum glutamic-pyruvic transaminase and alkaline phosphatase may be increased, but results were highly variable. Livers were pale and/or discolored. The following findings were noted during microscopic pathology: fibrosis and chronic inflammation of the thymus, erythroid/myeloid bone marrow depletion, inflammation and/or degeneration of the skeletal muscle, and liver changes (hepatocyte hypertrophy, biliary proliferation/hyperplasia, inflammation, and the presence of small vacuoles in the hepatocytes).

Acetylcholinesterase was decreased in the pons but not in the cerebellum nor in the erythrocytes. Inhibition ( $p \leq 0.05$ ) in the pons was 20% and 24% in males and 18% and 19% in females at 2 and 10 mg/kg/day, respectively. As a decrease was only noted in the pons (and not in the RBCs which is most sensitive in other studies) and the dose-dependency was questionable, the effect on the pons was considered an equivocal finding.

**The LOAEL for this study is 50 mg/kg/day based on increased mortality, clinical signs of toxicity, decreased body weight and food consumption, discolored liver, and several microscopic lesions (fibrosis and chronic inflammation of the thymus, erythroid/myeloid bone marrow depletion, inflammation and/or degeneration of the skeletal muscle, and liver changes). The NOAEL is 10 mg/kg/day.**

This study is classified **acceptable, non-guideline**. Excessive mortality was noted at the high dose, which means it does not satisfy the guideline requirement (OCSPP 870.4100b; OECD 452) for a chronic toxicity study in dogs. However, the study was otherwise conducted in a valid manner and provides meaningful results.

### **A.3.5 Carcinogenicity**

#### **870.4200a Carcinogenicity Study – Rat (see 870.4300)**

#### **870.4200b Carcinogenicity (feeding) - Mouse**

In a mouse oncogenicity study (**MRID 44161105**), bensulide ( $92.4 \pm 0.5\%$  a.i., Lot # CBI 0801) was administered for 78 weeks in the diet to 50 CD-1 mice/sex/dose at levels to achieve constant weekly doses of 0, 1, 50, or 200 mg/kg/day. An additional 10 mice/sex/dose were used to provide samples for plasma and red blood cell cholinesterase assessments at 13 weeks, and further cholinesterase assessments, including brain cholinesterase at 52 weeks; these animals were terminated and discarded at 52 weeks. All remaining animals were sacrificed at 78 weeks of the study.

Survival rates, clinical observations, and hematological parameters were unaffected by treatment with bensulide. Chronic toxicity was characterized by reduced ( $p < 0.01$  or  $< 0.001$ ) cholinesterase levels (plasma,  $\downarrow 92$ -96%; erythrocyte,  $\downarrow 40$ -51%) in the high-dose males and females and reduced brain cholinesterase in the high-dose females ( $\downarrow 14\%$ ). Additionally in the high-dose males, decreased overall body weight gains ( $\downarrow 32\%$ ;  $p < 0.001$ ), increased absolute and relative liver weights ( $\uparrow 38$ -43%;  $p < 0.001$ ), and histopathological changes of the liver (pale foci, cell atypia, and cell foci) were observed. In the 50 mg/kg/day animals, reduced ( $p < 0.01$ , or 0.001) plasma ( $\downarrow 88$ -92%) and RBC ( $\downarrow 31$ -37%) cholinesterase activities were observed and brain cholinesterase activity was reduced ( $\downarrow 12\%$ ;  $p < 0.05$ ) in the females. Additionally, overall body weight gain in the mid-dose males was reduced by 16% ( $p < 0.05$ ) compared to controls.

The chronic LOAEL is 50 mg/kg/day based on inhibition of plasma and erythrocyte cholinesterase activity in the 50 and 200 mg/kg/day group animals, inhibition of brain cholinesterase activity in the mid- and high-dose females, decreased body weight gain in the mid- and high-dose males, and increased liver weights, and histopathological

changes in the high-dose males. The chronic NOAEL is 1 mg/kg/day.

Under the conditions of this study, there was no evidence of carcinogenic potential.

Dosing was considered adequate based on decreased plasma, RBC, and brain cholinesterase activities, decreased body weight gains, and by increased liver weights and histopathological changes of the liver.

This study is classified as Acceptable/Guideline and satisfies the guideline requirements for a carcinogenicity study (§83-2b) in mice.

#### **870.4300 Combined toxicity/carcinogenicity – rat**

In a combined chronic/oncogenicity study (**MRIDs 43919602 and 44161101**), bensulide (92.4 ±0.5% a.i., Lot # CBI 0801) was administered in the diet for 104 weeks to 80 Sprague-Dawley rats/sex/group at levels to achieve constant weekly doses of 0, 1, 15, or 60 mg/kg/day. At approximately the 26, 52, and 78 week intervals, 10 rats/sex/group were terminated, and all remaining animals were sacrificed at 104 weeks of the study.

Survival rates, ophthalmoscopic findings, clinical observations, hematological parameters, urinalysis findings, and gross findings were unaffected by treatment with bensulide. Chronic toxicity in rats receiving 60 mg/kg/day was characterized in both sexes by reduced ( $p < 0.05$ ,  $< 0.01$  or  $< 0.001$ ) cholinesterase levels (plasma, ↓59-93%; erythrocyte, ↓44-80%; and brain, ↓20-39%) and, in the males, by increased absolute liver weights (↑4-22%) and mild histopathological changes of the liver (hepatocyte vacuolation and eosinophilic foci). In the 15 mg/kg/day animals, reduced ( $p < 0.05$ ,  $< 0.01$ , or  $0.001$ ) plasma (↓36-73%) and erythrocyte (↓20-40%) cholinesterase activities were also observed.

The chronic LOAEL is 15 mg/kg/day based on inhibition of plasma and erythrocyte cholinesterase activity in the mid- and high-dose group animals, inhibition of brain cholinesterase activity in the high-dose animals, and increased liver weights and mild histopathological changes in the high-dose males. The chronic NOAEL is 1 mg/kg/day.

Under the conditions of this study, there was no evidence of carcinogenic potential.

Dosing was considered adequate by decreased cholinesterase activity (plasma, red blood cell, and brain) in high-dose animals and by increased absolute liver weights and liver histopathological changes in the high-dose males.

This study is classified as Acceptable/Guideline and satisfies the guideline requirements for a chronic toxicity study (§83-1) and a carcinogenicity study (§83-2) in the rat.

#### **A.3.6 Mutagenicity**

The available studies clearly indicate that bensulide is not genotoxic. Additionally, the

negative mutagenicity studies support the lack of an oncogenic effect in the rat and mouse long-term feeding studies and also the absence of significant reproductive or developmental toxicity attributable to a mutagenic mode of action (i.e., decreased total implants, increased resorptions). Based on the overall results, there is no concern for mutagenicity.

The submitted test battery satisfies the new mutagenicity initial testing battery guidelines; therefore, no Category III study or additional further testing is required at this time.

In a reverse gene mutation assay in bacteria (**MRID 00153493**), strains TA98, TA100, TA1535, and TA1537 of *S. typhimurium* were exposed to bensulide technical (92.9% a.i.) at concentrations of 0 (dimethyl sulfoxide solvent control; DMSO), 0.005, 0.014, 0.041, 0.123, 0.370, 1.111, 3.333, 10.000, 25.000, or 50.000  $\mu\text{L}/\text{plate}$  (TA100) or 0 (DMSO), 0.037, 0.111, 0.333, 1.000, or 3.000  $\mu\text{L}/\text{plate}$  (TA98, TA1535, and TA1537) in the presence and absence of mammalian metabolic activation (metabolic activation mixture containing the S9 fraction from livers of Aroclor 1254-induced Sprague-Dawley rats).

Bensulide technical was tested up to and above levels at which it precipitated onto the culture medium ( $\geq 0.041 \mu\text{L}/\text{plate}$  for TA100;  $\geq 1.000 \mu\text{L}/\text{plate}$  for TA98, TA1535, and TA1537). The positive controls did induce the appropriate responses in the corresponding strains. There was no evidence of induced mutant colonies over background.

This study is classified as Acceptable/Guideline. It does satisfy the requirement for Guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

In a mammalian cell gene mutation assay (TK locus; **MRID 43273901**), mouse lymphoma L5178Y cultured cells cultured *in vitro* were exposed to bensulide technical ( $92.4 \pm 0.5\%$  a.i.; given in MRID 43919602) in dimethyl sulfoxide (DMSO) at concentrations of 8, 14, 16, 21, 24, 28, 32, 35, 40, or 42  $\mu\text{g}/\text{mL}$  in the absence and at 16, 24, 28, 32, 35, 40, 42, 48, 49, or 56  $\mu\text{g}/\text{mL}$  in the presence of mammalian metabolic activation (S9 fraction containing homogenate from Aroclor 1254-induced rat liver).

Bensulide technical was tested up to cytotoxic concentrations, based on preliminary cytotoxicity assays demonstrating significant cytotoxicity at doses near 30  $\mu\text{g}/\text{mL}$  and total cell death at doses as low as 25-30  $\mu\text{g}/\text{mL}$ . There was no evidence of induced forward mutation at the TK locus over solvent control values at any dose tested.

This study is classified as Acceptable/Guideline. It does satisfy the requirement for Guideline 84-2 for *in vitro* mutagenicity (gene mutation in mammalian cells) data.

In a C57BL/6JfCD-1/Alpk mouse bone marrow micronucleus assay (**MRID 41902602**), 5 animals/sex/dose were treated with a single oral (gavage) dose of bensulide technical (92.7% a.i.) in corn oil (vehicle) at doses of 250 or 400 mg/kg (constant dose volume of

10 mL/kg). Bone marrow cells were harvested at 24, 48 and 78 hours post- treatment.

There were no signs of toxicity during the study. Bensulide technical was tested at an adequate dose, since the 400 mg/kg dose level (HDT) was selected based on the results of a preliminary acute toxicity study (2 animals/sex/dose) in which mortalities were observed at doses of 500 mg/kg or greater, but not at 400 mg/kg or less. The positive control (cyclophosphamide) induced the appropriate response. There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time.

This study is classified as Acceptable/Guideline. It does satisfy the requirement for Guideline 84-2 for *in vivo* mutagenicity (mouse bone marrow micronucleus) data.

### A.3.7 Neurotoxicity

#### 870.6100 Delayed Neurotoxicity Study – Hen

In an acute delayed neurotoxicity study (**MRID 43334302**), Bensulide (tech., 92.4% a.i.) was assessed using groups of 15 single comb white leghorn laying hens (*Gallus gallus domesticus*) given a single neat gavage dose of Bensulide (2000 mg a.i./kg nominal dose; actual dose was 2262 mg/kg in a dosing volume of 2 mL/kg). An acute oral toxicity study (43306301) determined an LD<sub>50</sub> of 3221 mg/kg for Bensulide in the domestic laying hen. Positive controls (12 birds) were given 800 mg TOCP/kg and 12 birds given corn oil served as vehicle controls. Three birds of each group were sacrificed at -48 hrs for activity analysis of neurotoxic esterase (NTE) in brain and spinal cord and acetylcholinesterase (AChE) in brain. Behavior assessments (locomotor ability) were conducted on nine birds from both control groups and 12 birds from the Bensulide group over a period of 21 days. Pathology (brain, spinal column and peripheral nerves) was evaluated in all remaining animals at Day 21.

Based on the study results, Bensulide did not induce acute delayed neurotoxicity in the domestic laying hen at the dose tested. NTE activity was not affected by treatment. A non-significant decrease of -24% was observed for brain cholinesterase in treated hens.

This study meets the requirements of § 81-7 and is classified as Acceptable/Guideline because, although animals were not tested at the LD<sub>50</sub> and no signs of neurotoxicity were observed, animals were tested at the limit dose of 2 g/kg.

#### 870.6200 Acute Neurotoxicity Screening Battery

In an acute neurotoxicity screening study (MRID 43195901), 22 CD rats/sex/group were administered single gavage doses of 0, 30, 100 or 300 mg bensulide (tech., 92.4% a.i.)/kg (males) or 0, 15, 50 or 150 mg/kg (females) in 5 mL/kg corn oil. Functional observational battery (FOB) and motor activity tests were conducted on 12 rats/sex/dose pretreatment, on the day of dosing (day 0) and days 7 and 14 post-dosing. Plasma, erythrocyte and brain cholinesterase (ChE) activities were measured from 5

rats/sex at pretreatment, day 0 (6.25 and 6.75 hrs post- dosing) and day 15. Six perfused control and high dose rats/sex were evaluated for neuropathology.

At 150 mg/kg (females only), an increased incidence of diarrhea, flaccid abdominal and/or body tone (all 6/12 vs. 1, 2 and 2, controls) and pinpoint pupils (3/12 vs 0, controls) were observed on Day 0 in the FOB. At 300 mg/kg (males only), one death occurred on Day 1, preceded by clinical signs (salivation, lacrimation/ocular discharge, decreased respiration, hypothermia, and fur staining on muzzle and ventral surface). A second male exhibited abnormal respiration, tremors, hypoactivity, dehydration and fur staining between Days 1-3. In the FOB, increased incidence of decreased arousal and locomotor activity (for both, 7/12 vs. 3, controls) were observed. A slight but statistically significant depression of body weight (-6.6%) was also observed on Day 7. No treatment-related effects on motor activity or macroscopic/microscopic neuropathology were reported. The LOAEL is 150 mg/kg, based on minimal, transient clinical signs consistent with cholinesterase inhibition in females. The NOAEL is 100 mg/kg.

At 50 mg/kg (females only), plasma ChE was decreased on day 0 by 80% less than controls (not significant). At 100 mg/kg (males only), plasma ChE was decreased on day 0 by 53% (not significant). At 150 mg/kg (females only) on day 0, reductions were observed in plasma ChE (89% less than controls,  $p < 0.01$ ) and erythrocyte ChE (37% less than control,  $p < 0.01$ ) both of which showed partial recovery by day 15. However, a significant decrease (73% of control,  $p < 0.01$ ) in brain ChE for high-dose females was noted on day 15 which was not present at day 0 (18% less than controls, not significant). At 300 mg/kg (males only), statistically significant ChE inhibition was observed only in the high-dose groups. On day 0, there were significant decreases in brain ChE (62% of control,  $p < 0.01$ ), plasma ChE (19% of control,  $p < 0.01$ ), and erythrocyte ChE (60% of control,  $p < 0.01$ ) for males of the high dose (300 mg/kg) group. At day 15, brain ChE was still significantly reduced (73% of control,  $p < 0.01$ ) but values for plasma and erythrocyte ChE had returned to normal.

The plasma ChE inhibition LOAEL is 50 mg/kg, based on 80% inhibition (no p) of plasma cholinesterase activity in females on Day 0. The plasma ChE NOAEL is 15 mg/kg.

The RBC ChE inhibition LOAEL is 150 mg/kg, based on 37% inhibition ( $p \leq 0.01$ ) of RBC ChE activity in females on Day 0. The RBC ChE NOAEL is 50 mg/kg.

The brain ChE inhibition LOAEL is 150 mg/kg, based on 18% inhibition (no p) of brain ChE activity in females on Day 0 and 27% inhibition ( $p \leq 0.01$ ) on Day 15. The brain ChE NOAEL is 50 mg/kg.

This study is classified as Acceptable/Guideline and satisfies the guideline requirement for an acute neurotoxicity study in rats (§81-8ss).

**870.6200 Subchronic Neurotoxicity Screening Battery (Not Submitted; Not Required – Waived; Leshin, 2015, TXR # 0057280)**

**870.6300 Developmental Neurotoxicity Study (Not Submitted; Not Required – Waived; Leshin, 2015, TXR # 0057280)**

### **A.3.8 Metabolism**

#### **870.7485 Metabolism – Rat**

In a metabolism study (MRIDs 42007901-42007904), bensulide technical, labelled with  $^{14}\text{C}$  in the phenyl ring (> 96.4% radiopurity; 925 MBq/mMole) was dissolved in corn oil (vehicle) and administered to Sprague-Dawley rats (5/sex/group; 7-8 weeks of age; 185-235 g body weight) following three treatment regimes. Animals in Group I received a single oral dose of radioactive bensulide at 1 mg/kg of body weight. Animals in Group II received 14 consecutive doses (1 mg/kg/day) of non-radioactive bensulide technical (99% a.i.) in corn oil, followed by a 1 mg/kg dose of radiolabelled bensulide technical in corn oil on day 15. Group III animals received a single oral dose of radiolabelled bensulide technical at 100 mg/kg of body weight. An additional group of animals (Group IV; 3/sex/group) were given a single oral dose of radiolabelled bensulide technical at 1 mg/kg of body weight and were subsequently used for autoradiological radiolabelled carbon dioxide release determinations. Administration by gavage was used for all treatment groups, and the volume of the corn oil and bensulide technical solution was kept at a constant of 4mL/kg of body weight.

For animals in Groups I-III, urine and feces were collected at 12, 24, 36, and 48 hours post-dosing and at 24- hour intervals thereafter until 7 days after dosing with radioactive bensulide. All animals in Groups I-III were sacrificed 7 days after treatment with radioactive bensulide technical, and the following organs were removed and assayed for radioactivity: blood, liver, kidneys, muscle, fat lungs, uterus, heart, bone, spleen, thyroid, salivary glands, brain, adrenals, ovaries, testes, pancreas, gastrointestinal tract (stomach, small and large intestines, and caecum) and its contents, and the residual carcass. Radioactivity was determined by tissue combustion and/or liquid scintillation counting. For Groups IV animals, two rats of each sex were used for the autoradiography study and 1 rat of each sex was used for the carbon dioxide study.

In the autoradiography study, animals were sacrificed with Halothane at 24 hours after dosing with radioactive bensulide technical. The animals were then immediately frozen in a mixture of hexane and solid carbon dioxide. Each frozen carcass was embedded in a block of 2% carboxymethyl cellulose, and longitudinal sagittal section of about 20  $\mu\text{M}$  thickness were cut and representative sections freeze-dried and subjected to autoradiography. In the carbon dioxide study,  $^{14}\text{C}$ -radiolabelled derived from the metabolism of radioactive bensulide technical and present in expired air was collected by passing the air through a 2N NaOH solution at 6, 12, 24, 36, and 48 hours after dosing.

The major route of excretion was via the urine, with peak urinary excretion of  $^{14}\text{C}$ -bensulide equivalents occurring between 0 to 24 hours for males and females in the low-dose group (Group I; 1 mg/kg) and in the high-dose group (Group III; 100 mg/kg). In Group I, total urinary excretion of 7 days after administration of radioactive bensulide technical accounted for 70 and 75 percent of the administered dose in males and females, respectively. Of these totals, 57 and 72 percent were excreted during the first 24 hours after dosing for males and females, respectively. In Group III, total urinary excretion accounted for 75 and 87 percent of the administered dose in males and females, respectively. Of these totals, 64 and 76 percent were excreted during the first 24 hours after dosing for males and females, respectively.

For Group II (prior 14-day administration of non-radioactive bensulide technical before radioactive bensulide administration, both at 1 mg/kg), total urinary excretion of radioactivity over 7 days past dosing with radioactive bensulide accounted for 79 and 88 percent of the administered dose in males and females, respectively. Of these totals, 63 and 83 percent were excreted during the first 24 hours after dosing for males and females, respectively. For Group IV, urinary excretion of  $^{14}\text{C}$  radioactivity derived from bensulide technical over a 48-hour period accounted for 67% for one male and 86% in one male.

For Group I, total fecal excretion of radioactivity derived from  $^{14}\text{C}$ -bensulide technical over 7 days post-dosing accounted for 22 and 20 percent of the administered dose in males and females, respectively. Of these totals, 18 percent was excreted during the first 24 hours for both males and females. For Group III, total fecal elimination over 7 days post-dosing of bensulide-derived radioactivity accounted for 22 and 11 percent of the administered dose for males and females, respectively. Of these totals, 20 and 8 percent were excreted during the first 24 hours after dosing for males and females, respectively. In Group II animals, total fecal excretion of radioactivity over 7 days post-dosing accounted for 14 and 8 percent of the administered dose for males and females, respectively. Of these totals, 9 and 6 percent were excreted during the first 24 hours post-dosing for males and females, respectively. In Group IV, fecal excretion of radioactivity over 48 hours post-dosing accounted for 12% of the administered dose in one male and 7% in one female.

The amount of residual radioactivity in all organs/tissues except for the liver (0.02 to 0.21% of the dose) from all rats was low at 7 days after single oral administration of radioactive bensulide technical. The radioactivity found in the carcasses and in other tissues accounted for 0.3% to 2.5% and less than 0.1% of the administered dose, respectively. The highest concentration of radioactivity was found in whole blood. The majority of the radioactivity in the blood was associated with the cellular component. In general, less well perfused tissues showed lower concentrations of radioactivity. Whole body autoradiography of rats killed 24 hours after dosing showed that, in male rats, the majority of the radioactivity was present in the blood, lung, spleen, bone marrow, and the glandular part of the stomach, the contents of the intestines, and in the intestinal walls. Moderate amounts of radioactivity was found in the liver, kidney, salivary glands,

the capsule of the seminal vesicles, nasal passages and the white matter of the brain. The intensity of radioactivity in the female rats was much lower than in the male rats.

In a biotransformation study (MRID 42225401), bensulide metabolites were quantitated and identified in rat urine and fecal extracts from previous studies (MRID 42007901-42007903). To obtain sufficient material to confirm metabolite identities, four successive daily doses of 50 mg [ $^{14}\text{C}$ ]-bensulide/kg were administered to 5 Sprague-Dawley female rats (bulk collection experiment; 99% a.i., unlabeled, Batch No. Y06379/006; >98.0% a.i., [ $^{14}\text{C}$ ]-labeled, Batch No. Y06379/005). Biliary excretion was assessed in one male and one female rat with cannulated bile ducts given an oral dose of 100 mg [ $^{14}\text{C}$ ]-bensulide/kg.

No animals died before scheduled sacrifice in either experiment. In the bulk collection experiment, 52.5% of the administered dose was recovered in the urine and 16.3% in the feces. In cannulated rats, a substantially higher fraction of the given dose was in the feces (40.9% in the male, 68.6% in the female), possibly due to poor intestinal wall absorption. Biliary excretion was minimal (5-6% of dose) and biliary metabolites were not analyzed; the mass balance accounting was acceptable (109.2%-114.4%).

Bensulide metabolites found by TLC in excreta from previous studies accounted for about 59-78% of the administered dose in the urine and about 2.5-8.3% in the feces, distribution varying with sex and dose. Four metabolites were identified. Metabolite I was the most abundant in the urine for all doses in both sexes (26-58% of given dose) whereas in fecal extracts, Metabolites I, II, or IV predominated (each 0.25-3.4% of dose). Unidentified metabolites individually represented < 3% of the dose except urinary metabolite "H" ( $\leq 16.1\%$  of dose) and one fecal metabolite (TLC spot 6;  $\leq 6.23\%$  of dose). Metabolite I and II formation is proposed to involve cleavage of the  $\text{PO}_2[\text{CH}(\text{CH}_3)_2]_2$  moiety of bensulide, followed by methylation and oxidation of the sulphur atom. Conjugation with glycine or carboxylation and oxidative desulphuration is proposed to lead to Metabolite III and IV formation, respectively.

This study is classified acceptable/guideline. It was intended to satisfy the guideline requirement for a metabolism study (§85-1) in rats together with four previous studies (MRIDs 42007901-42007904). Together these metabolism studies satisfy the Guideline (§85-1) requirements for metabolism data for bensulide technical in rats.

#### **870.7600 Dermal Absorption – Rat (Not Submitted; Not Required)**

### A.3.9 Immunotoxicity

#### 870.7800 Immunotoxicity

In an immunotoxicity study (MRID 48377701), bensulide (94.12% a.i., Lot No. TQ-BTS1001-019) in 1% methyl cellulose in water was administered via gavage to female B6C3F1 mice (8/group) at dose levels of 0, 50, 200, or 800 mg/kg/day for 28 days. The female mouse was selected as the default species/sex for immunotoxicity study. Cyclophosphamide (positive control) was injected intraperitoneally at a dose of 80 mg/kg approximately 24 hours prior to sacrifice. On study day 25, each mouse was immunized with sheep red blood cell (SRBC) via an intraperitoneal injection ( $2 \times 10^8$  SRBC/animal). On Day 29, T-cell dependent antibody response (TDAR) was determined with an anti-SRBC plaque forming cell (PFC) assay.

Two animals in the 800 mg/kg/day group died. These animals demonstrated labored breathing, hypoactivity and were cold to the touch. The gross necropsy indicated that these deaths were due to toxic response to bensulide. There was an overall weight gain in all dose groups and the vehicle control group. The body weight changes did not indicate any remarkable departures from normal animal growth or feeding behavior. The mean absolute and relative spleen and thymus weights of animals in the test groups did not show significant differences from controls.

The results of the TDAR were considered unacceptable. The performing laboratory did not follow the original study protocol. The amended procedure stated that additional rabbit anti-mouse IgG was added to one of the duplicate tubes containing the splenocytes, sheep red blood cells and guinea pig complement to allow the detection of IgG secreting PFCs in addition to the IgM secreting PFCs. The total PFCs per  $10^6$  cells was then calculated by combining PFC of two tubes together. The principle of the anti-SRBC PFC assay is to measure the effect of test substance on the anti-SRBC IgM secreting cells. The addition of IgM PFCs and IgG PFCs from both tubes as the total plaques formation was misleading and flawed. Nonetheless, the procedures for measuring IgG secreting cells and interpretation of data in this study were incorrect. Detailed comments are described in the reviewer's comment section of this DER.

In addition, the responsiveness of the immunization in this study was questionable. The study report claimed the response of the vehicle control animals exceeded the minimum expectations (800 total plaques/ $1 \times 10^6$  spleen cells) by combining both tubes including the IgM PFCs and the IgG PFCs. This statement was incorrect because the stated IgG PFC tube would already have included IgM and IgG PFCs; it would be double counting if combining both tubes. The purpose of the duplicate tubes was to obtain an average of the PFCs formation for each spleen. The individual animal data in this study on the IgM plaques formation indicated that the animals had not been properly stimulated after SRBC injection (e.g., only one animal in the vehicle control group responded with greater than 800 PFCs per  $10^6$  cells). The results suggested that antigen (SRBC) might have been accidentally injected into the intestinal tract.

The report of the study suggests that the performing laboratory lacks understanding of the immunotoxicity study. The performing laboratory needs to establish a standard operation procedure (i.e., test procedures, SRBC antigen injection technique by i.v. or i.p., and establish optimum amount of complement to be added to the assay tube) and validate its proficiency.

This immunotoxicity study in mice is **Unacceptable/guideline** and does not satisfy the guideline requirement for an immunotoxicity study (OPPTS 870.7800). This data requirement was waived by HASPOC (van Alstine, 2013, TXR # 0056738).

### A.3.10 Special/Other Studies

#### Non-guideline Comparative Cholinesterase Assay – Rat

The purpose of this non-guideline study was to identify any sensitive populations that may exist (pregnant females, immature (PND 11) rats, or fetuses) to the cholinesterase (ChE) inhibitory effects of bensulide, an organophosphate. Toxicity was evaluated in each of these lifestages/sub-populations and compared to adults. Both acute and repeated dose regimens were evaluated, as well as treatment during the organogenesis and fetal phases of pregnancy (gestation day [GD] 6-20).

In the acute study (MRID 49433502), young adult Sprague-Dawley rats and PND 11 pups (10/sex/dose) were treated by a single gavage (5 mL/kg) dose with bensulide in corn oil. The dose groups were 0, 50, 100, 150, and 200 mg/kg/day in the adult males, 0, 25, 50, 100, and 150 mg/kg/day in adult females, and 0, 20, 40, 60, and 100 mg/kg/day in the pups.

In the repeated dose study (MRID 49466201), young adult Sprague-Dawley rats and PND 11 pups (10 adult females/dose [no male adults] and 10 pups/sex/dose) were treated by gavage (5 mL/kg) with bensulide in corn oil. The dose groups were 0, 15, 25, 50, and 75 mg/kg/day in the adults and 0, 5, 10, 20, 40, and 60 mg/kg/day in the pups. Animals were treated once daily for 10 consecutive days.

In the gestational study (MRID 49454001), adult Sprague Dawley rats were bred and pregnant females (10/dose) were treated by gavage (5 mL/kg) with bensulide in corn oil once daily during GD 6-20 (inclusive). The dose groups were 0, 15, 30, 60, and 90 mg/kg/day.

In all studies, blood and brain samples were collected at the time of peak effect, previously determined to be 16 hours after treatment of adults and pups. Samples were processed and assayed for cholinesterase levels by the modified Ellman's method. Additionally, mortality and clinical signs were evaluated in the acute study. Body weights were also evaluated in the repeated and gestational studies. A necropsy was also performed on all animals in the gestational study only.

In all studies, no adverse treatment-related effects were noted on mortality, clinical signs, body weight, body weight gains, or gross pathology (gestational study).

Dose-dependent decreases in cholinesterase activity were observed in the brain and RBC in all three studies.

In the acute study, decreases ( $p \leq 0.01$ ) in cholinesterase activity were noted as follows: (i) adult male RBC at 100 mg/kg/day and above ( $\downarrow 22$ -69%); (ii) adult female RBC at 50 mg/kg/day and above ( $\downarrow 26$ -89%); (iii) adult male brain at 100 mg/kg/day and above ( $\downarrow 14$ -46%); (iv) adult female brain at 50 mg/kg/day and above ( $\downarrow 12$ -62%); (v) PND 11 male pup RBC at 40 mg/kg/day and above ( $\downarrow 32$ -78%); (vi) PND 11 female pup RBC at 40 mg/kg/day and above ( $\downarrow 31$ -77%); (vii) PND 11 male pup brain at 40 mg/kg/day and above ( $\downarrow 20$ -57%); and (viii) PND 11 female pup brain at 40 mg/kg/day and above ( $\downarrow 19$ -58%).

In the repeated dose study in the adult female RBC, dose-related increases ( $p \leq 0.01$ ) in ChE inhibition were observed at 25 mg/kg/day and above ( $\downarrow 22$ -91%). Decreases ( $p \leq 0.01$ ) in adult female brain cholinesterase activities were noted at 50 mg/kg/day and above ( $\downarrow 51$ -69%). In the pups, decreased ( $p \leq 0.01$ ) RBC cholinesterase activity were noted in males at 10 mg/kg/day and above ( $\downarrow 13$ -71%) and in females at 20 mg/kg/day and above ( $\downarrow 35$ -72%). Decreased ( $p \leq 0.01$ ) pup brain cholinesterase activity were noted in males at 20 mg/kg/day and above ( $\downarrow 11$ -46%) and females at 40 mg/kg/day and above ( $\downarrow 33$ -42%).

In the gestational study in the dam RBC, dose-related increases ( $p \leq 0.01$ ) in ChE inhibition were noted at 30 mg/kg/day and above ( $\downarrow 52$ -99%). Dam brain ChE inhibition ( $p \leq 0.01$ ) was also observed at 30 mg/kg/day and above ( $\downarrow 19$ -84%). In the fetal RBC, dose-related increases ( $p \leq 0.01$ ) in ChE inhibition were noted at 30 mg/kg/day in both sexes ( $\downarrow 20$ -92%). In the fetal brain, dose-related increases ( $p \leq 0.05$ ) in ChE inhibition were also noted in both sexes at 30 mg/kg/day and above ( $\downarrow 9$ -49%), with the males being slightly more sensitive than females.

**In the acute study, the LOAEL in adults was 50 mg/kg/day based on ChE inhibition in the RBC and brain of females. The NOAEL was 25 mg/kg/day. The LOAEL in the PND 11 pups was 40 mg/kg/day based on ChE inhibition in the RBC and brain of males and females. The NOAEL was 20 mg/kg/day.**

**In the repeated dose study, the LOAEL in adults was 25 mg/kg/day based on ChE inhibition in the RBC of females (only sex tested). The NOAEL was 15 mg/kg/day. The LOAEL in the PND 11 pups was 10 mg/kg/day based on ChE inhibition in the RBC of males. The NOAEL was 5 mg/kg/day.**

**In the gestational study, the LOAEL in dams and fetuses was 30 mg/kg/day based on ChE inhibition in RBC and brain. The NOAEL was 15 mg/kg/day.**

This study is **acceptable and** fulfills the purpose of this non-guideline study. The study identified sensitivity (or lack thereof) in sub-populations (pregnant females, immature (PND 11) rats, or fetuses).

#### Appendix A.4. Lifestage Sensitivity to Bensulide-Induced Acetyl Cholinesterase (AChE) Inhibition in the RBC of Rats Following Oral Treatment

MRID # Test	Lifestage Sex	BMD <sub>10</sub> (mg/kg/day)	Nearest Dose to 90% of Control (% of Control)	Fold- Difference <sup>b</sup>	Conclusion
Acute <sup>a</sup>					
Pup vs Adult					
49433502 Acute CCA	Adult Male	79.11	50 (99%) 100 (78%)	4.5	The pup is more sensitive than the adult.
49433502 Acute CCA	Pup (PND 11) Male	17.74	20 (91%)		
49433502 Acute CCA	Adult Female	27.21	25 (95%) 50 (73%)	1.7	The pup is more sensitive than the adult.
49433502 Acute CCA	Pup (PND 11) Female	16.23	20 (88%)		
Steady State					
Pup vs Adult					
49466201 Repeated Dose CCA	Adult Female	18.66	15 (94%) 25 (78%)	1.5	The pup is more sensitive than the adult.
49466201 Repeated Dose CCA	Pup Female	12.30	5 (93%)		
Fetus vs Dam					
49454001 Gestational CCA	Dam	12.01	15 (94%) 30 (48%)	Dam vs male fetus: 0.5	The fetus is not more sensitive than the mother.
49454001 Gestational CCA	Male Fetus	22.34	15 (101%) 30 (80%)	Dam vs female fetus: 0.6	
49454001 Gestational CCA	Female Fetus	21.82	15 (100%) 30 (80%)		
Pregnant vs Non-Pregnant					
49454001 Gestational CCA	Dam	12.01	15 (94%) 30 (48%)	0.6	The pregnant female is not more sensitive than the non- pregnant female at doses relevant to risk assessment. The level of acetylcholinesterase inhibition was exactly the same at 15 mg/kg/day and the steady-state POD is 6 mg/kg/day.
49466201 Repeated Dose CCA	Adult Female (Not Pregnant)	18.66	15 (94%) 25 (78%)		

<sup>a</sup> No data available to compare fetus vs dam or pregnant vs non-pregnant lifestages following a single dose.

<sup>b</sup> Upper Row ÷ Lower Row of Merged Cell. When BMD did not agree with empirical evidence, the dose tested which provided inhibition nearest 10% was used instead of BMD<sub>10</sub>.

**Appendix B. Physical/Chemical Properties**

<b>Table B1. Physicochemical Properties of Bensulide and Bensulide Oxon</b>		
Parameter	Value	Reference
<b>Bensulide</b>		
Molecular weight (g/mole)	397.54	MRID 45761801
Melting point (°C)	36	MRID 41532001
Water solubility ( mg/L at 25°C)	5.6	MRID 41532001
Vapor pressure at 25°C (mmHg)	$8.2 \times 10^{-7}$	MRID 41532001
Dissociation constant (pK <sub>a</sub> )	Not Applicable	
Octanol/water partition coefficient Log(K <sub>OW</sub> )	4.20	H. Zhong, D428601, 09/14/2015 (values modeled with EPI Suite, v 4.10)
<b>Bensulide oxon</b>		
Molecular weight (g/mole)	381.44	H. Zhong, D428601, 09/14/2015 (values modeled with EPI Suite, v 4.10)
Melting point (°C)	89.97	
Water solubility ( mg/L at 25°C)	461.24	
Vapor pressure at 25°C (mmHg)	$2.48 \times 10^{-8}$	
Dissociation constant (pK <sub>a</sub> )	Not Applicable	
Octanol/water partition coefficient Log(K <sub>OW</sub> )	2.35	

**Appendix C. Review of Human Research**

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1), the Agricultural Handler Exposure Task Force (AHETF) database and, the Aquatic use Standard Operation Procedure (20-Sep-2013) and are subject to ethics review pursuant to 40 CFR 26, have received that review, and are compliant with applicable ethics requirements. For certain studies that review may have included review by the Human Studies Review Board. Descriptions of data sources as well as guidance on their use can be found at <http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data> and <http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure>.

**Appendix D. International Residue Limits Table****Bensulide (PC Code 009801)**

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico <sup>2</sup>	Codex
40 CFR 180.241: (a) General. (1) -(O,O-diisopropyl phosphorodithioate) of N-(2-mercaptoethyl) benzenesulfonamide including its oxygen analog S-(O,O-diisopropyl phosphorothioate) of N-(2-mercaptoethyl) benzenesulfonamide		None		None
Commodity <sup>1</sup>	Tolerance (ppm) /Maximum Residue Limit (mg/kg)			
	US	Canada	Mexico <sup>2</sup>	Codex
Onion, bulb	0.10			
Vegetable, brassica, leafy group 5	0.15			
Vegetable, cucurbits group 9	0.15			
Vegetable, fruiting group 8	0.10			
Vegetable, leafy except brassica group 4	0.15			
Completed: M. Negussie; 09/21/15				

<sup>1</sup> Includes only commodities of interest for this action. Tolerance values should be the HED recommendations and not those proposed by the applicant.

<sup>2</sup> Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

(c) Tolerances with regional registrations. Tolerances with regional registration, as defined in §180.1(l), are established for the residues of S-(O,O-diisopropyl phosphorodithioate) of N-(2-mercaptoethyl) benzenesulfonamide including its oxygen analog S-(O,O-diisopropyl phosphorothioate) of N-(2-mercaptoethyl) benzenesulfonamide in or on the following food commodities:

Commodity	Parts per million
Carrot, roots	0.10

## Appendix E. Comparison of Residue Levels of Bensulide and its Oxon

Table E summarizes residue data for commodities that do not have PDP data available for both parent bensulide and its oxon. The purpose is to provide information to address the dietary exposure and risk assessment. In addition, PDP data for lettuce (in which bensulide and its oxon were measured) were included.

<b>Matrix (Reference)</b>	<b>Use Pattern / PDP Sample ID</b>	<b>Bensulide</b>	<b>Bensulide Oxon</b>	<b>Factor (Oxon/Parent)</b>
Tomato Metabolism (D179576, 04/21/1993)	8.6 lbs ai/A pre-plant 112-153 day PHI	ND (86% TRR iden/char)	ND (86% TRR iden/char)	NA
Lettuce Metabolism (D1855889, 03/29/1993)	8.6 lbs ai/A soil pre-plant 67 day PHI	ND (86% TRR extracted)	2% TRR (86% TRR extracted)	NA
Carrot Metabolism (D177460, 06/02/1992)	8.6 lbs ai/A soil pre-plant 126 day PHI	30% TRR (94% TRR extracted)	2.8% TRR (94% TRR extracted)	0.09x
Squash Field Data (D218256, 01/24/1996)	9 lbs ai/A pre-plant	ND <sup>1</sup>	ND <sup>1</sup>	NA
Cucumber Field Data (D218256, 01/24/1996)	9 lbs ai/A pre-plant	ND <sup>1</sup>	ND <sup>1</sup>	NA
Bulb Onion (D206633, 11/29/1994)	9 lbs a.i./A pre-plant or pre-emergence Harvest at Maturity	ND <sup>1</sup>	ND <sup>1</sup>	NA
Bell Peppers (D238521, 10/07/1997)	5-9 lbs ai/A pre-plant or pre-emergence 109-129 day PHIs	ND <sup>1</sup>	ND <sup>1</sup>	NA
Lettuce PDP Results (years 2010-2011)	2010-6721	0.005	0.01	2.0
	2010-6845	0.004	0.005	1.3
	2010-7044	0.014	0.12	8.6
	2010-7052	0.005	0.008	1.6
	2010-7265	0.014	0.023	1.6
	2011-6295	0.012	0.003	0.3

<sup>1</sup> The LOQ is reported to be 0.05 ppm.

**Lettuce:** The metabolism study with lettuce showed detection of the oxon but not of the parent bensulide which suggest that the oxon may predominate. PDP data for lettuce (years 2010 and 2011) shows that bensulide ( $\text{LOD} \leq 0.014$  ppm) was detected in 6 of 1487 samples whereas bensulide oxon ( $\text{LOD} \leq 0.002$  ppm) was detected in 49 of those 1487 samples. The samples in which both were detected were included in the table above in order to estimate the ratio of the concentration of the oxon with respect to parent bensulide. These factors range from 0.3 to 8.6. This data suggest a factor of 9x for oxon residues with respect to bensulide.

**Other Crops (Non-Leafy):** The metabolism study with tomato and carrot and the crop field trial data do not suggest that parent bensulide or the oxon may be present at significant concentrations. PDP data with summer squash, carrot and tomato was generated for bensulide and its oxon. Only two sample of tomato showed bensulide being detected; however, there were not detects of the oxon. This suggest that both residues of concern would be at low concentrations and that the oxon do not seem to predominate in these crops.